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AGE	Under 18	18-22	23-27	28-32	33-37	38-42	43-47	48-52	53-57	58-62	63 +
SYSTOLIC Male	117.0	120.2	121.2	121.8	122.9	124.3	126.0	128.1	130.3	131.9	134.2
Female	114.7	116.4	117.7	118.7	120.4	123.6	127.1	129.8	132.5	133.7	135.4
DIASTOLIC **Male	76.4	78.1	78.8	79.5	80.4	81.4	82.3	83.3	84.3	84.5	84.0
Female	75.8	77.1	78.0	78.6	79.9	81.9	83.9	85.4	86.8	86.8	84.4

**Fourth phase

*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MAY, 1954

ORIGINAL ARTICLES

THE STOMACH IN PERNICIOUS ANEMIA: A CYTOLOGIC STUDY*

By Barbara W. Massey, A.B.
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In the course of a series of cytologic examinations for the detection of gastric malignancy, a positive report was made on a patient with treated pernicious anemia. Subsequent clinical observations did not confirm this diagnosis. Because of the puzzling cells in this case an effort was made to collect gastric smears on all available patients with treated pernicious anemia. At the time the study was undertaken it was felt that the cells in this patient, although not in all respects characteristic, were nevertheless diagnostic of carcinoma. They were much larger than normal, varied in size, and had heavy nuclear membranes (Fig. 10). Cells of such size and nuclear abnormality had not been seen before in this laboratory except in malignant stomachs.

The available evidence indicates that pernicious anemia is but one manifestation of a systemic disease caused by a nutritional deficiency secondary to an atrophic gastric mucosa. Replacement therapy corrects the metabolic defect in the nervous system and the blood; however, the gastric changes remain. Clinically this is evidenced by the persistence of achylia gastrica and the increased incidence of gastric carcinoma and polyposis[2,18,20,21,24,26,27,30,31]. Gastric biopsies[11,25,28] and several excellent pathologic studies[10,12,13,14,19,22,23,32] demonstrate the permanence of glandular atrophy.

Thus this study was undertaken not only to explain an apparent false positive diagnosis, but also to gather additional knowledge about the stomach in these cancer prone patients.

Material and Methods. Smears were collected from the stomachs of 21 patients with treated pernicious anemia in complete hematologic remission. The

*Presented October 30th, 1953 at the Central Society for Clinical Research, Chicago, Illinois. This study was facilitated by the Illinois Branch of the American Cancer Society and the Stewart Fund Grant to the University of Chicago.

†Present address: Department of Medicine, University of Washington, Seattle 5, Washington.

TABLE 1.—CLINICAL DATA

Name and Unit No.	Date	Sex	Age	Duration of Symptoms	Duration of Adequate Treatment	Free HCl After Histamine	Bone Marrow	Peak Reticulocyte Count—%	Day of Peak Retic. Count—After Start of Therapy	Hemoglobin in Grams	Red Blood Count in Millions	Blood Smear	Posterior Column Signs	Lateral Column Signs	Pallor	Atrophic Tongue	Palpable Spleen	Palpable Liver	Gastric Polyps on Gastroscopy	Gastric Polyps on X-ray	"P. A. Cells"	Active "P. A. Cells"	Goblet Cells	Thin Cells
J. B.	4/47	M	30	2 yrs.	6 yrs.	—	meg.	0	0	12.3	2.7	maer.	+	—	+	—	—	+		—				
406406	10/50									14.9	4.3	norm.	—	—					—	—				
	9/52									15.5	4.3	norm.							—		—		—	+
	10/53																		—		+		—	
V. B.	12/43	F	52	6 mos.	10 yrs.	—	0	75→2	14	10.5	2.2	maer.	+	+	+	+	—	—		—				
322501	12/51									14.6	4.7	norm.								—				
	3/53									13	4.0	norm.	—								+	+	—	—
T. C.	1/46	M	61	1 yr.	7 yrs.	—	meg.	2.7→10.3	16	12.2	2.8	maer.	—	+	—	—	—	—		—				
374051	1/53												—	+							+	+	—	+
R. D.	2/33	F	44	2 yrs.	20 yrs.	—	0	1.3→15	4	9.5	2.1	maer.	+	—	—	+	—	+						
76930	11/40					—				13.2	4.9	norm.							—	—				
	1/43																			—				
	1/47																			—				
	1/50																			—				
	11/52																			—	+	+	—	+
	5/53									13.1	4.1	norm.							?+	+				
	10/53																		—					
L. E.	10/43	F	32	9 mos.	10 yrs.	—	0	2.1→5	6	11.0	2.8	maer.	—	—	—	—	—	+	—	—				
320038	12/48									14.0	4.5	norm.							—	—				
	2/53									12.5	4.2	norm.							—		+	—	+	+
E. F.	1/38	M	45	2 yrs.	15 yrs.	—	0	5→9.5	6	9.5	2.5	maer.	—	—	+	—	—	+		—				
190840	4/43					—				14.3	4.4	norm.							—	—				
	9/52									13.1	4.0	norm.	—	—						—	—	—	—	—
	8/53									13.8	4.3	norm.								—	—	—	—	—
	11/53																		—	—	+	—	—	—
B. G.	6/50	F	40	4 yrs.	3 yrs.	—	meg.	3.8→9.2	10	5.4	1.3	maer.	—	—	+	+	—	+		—				
493201	8/51									12.5	4.1	norm.								—				
	3/53									14.7	4.5	norm.							+	—	+	—	—	—
	6/53																				+	—	—	—
R. H.	12/51	F	26	1 mo.	2 yrs.	—	meg.	2.1→22.9	6	5.0	0.9	maer.	+	—	—	—	+	—						
537897	3/53																				+	—	—	—
	7/53																		+	+				
	11/53									12.6	4.0	norm.	—	—							+†	—	—	—
H. H.	6/47	M	49	1 yr.	6 mos.	—	eryth. & some meg.*	1.5→3.4	5	14.0	3.9	maer.	+	+	+	+	+	—		—				
410954	8/48									15.3	4.8	norm.	—	+										
	3/49																			—				
	12/50																			—				
	2/52									14.0	4.5	norm.	—	—										
	2/53									15.8	4.9	norm.							—		+	+	—	—
I. J.	8/50	F	32	6 mos.	3 yrs.		meg.	1→17.6	8	6.2	1.9	maer.	—	—	+	+	—	—						

	3/49																								
	12/50																								
	9/52																								
	2/53									14.0	4.5	norm.	–	–											
										15.8	4.2	norm.							–		+	+	–	–	
L. J.	8/50	F	32	6 mos.	3 yrs.	–	meg.	1→17.6	8	6.2	1.9	macr.	–	–	+	+	–	–		–					
440758	4/51									13.8	4.8	norm.							–						
	8/52									13.6	4.1	norm.							–	–	+	–	–	–	
L. L.	4/53	F	62	8 mos.	6 mos.	–	meg.	1.6→6.9	9	11.2	2.5	macr.	–	–	–	+	–	+	+	+					
560107	5/53																				+	+	–	+	
	7/53									13.1	4.1	norm.													
	11/53																				+†	–	–	–	
J. M.	7/48	M	50	1 yr.	5 yrs.	–	meg.	0	0	12.0	3.9	macr.	+	+	–	+	–	–	–	–					
71105	5/49									13.5	4.0	norm.	+	+						–					
	6/51									15.5	5.1	norm.								–					
	6/53									14.0	0	0	+	–					?+		+	–	–	–	
A. M.	9/51	M	67	9 mos.	2 yrs.	–	meg.	1.8→16.2	12	8.2	2.4	macr.	–	–	–	–	–	–	–	–					
204838	12/52																		–		–	–	–	–	
	3/53									13.8	4.3	norm.							+	–	+	+	–	–	
W. N.	7/50	M	44	3 mos.	3 yrs.	–	meg.	.7→15.3	10	10.0	2.6	macr.	+	–	–	–	–	+	+	–					
496066	3/52									16.5	5.3	norm.	–	–					+	–					
	4/53									16.1	5.3	norm.	–	–					+	–	+	+	–	–	
	5/53																		+						
A. R.	11/30	M	26	3 mos.	22 yrs.	–	0	1.2→18	11	5.0	1.3	macr.	–	–	+	–	+	–		–					
31249	10/37					–				14.2	4.1	norm.							–						
	7/38									13.5	4.8	norm.							–						
	7/40									12.5	5.0	norm.							–						
	2/50									13.5	4.1	norm.							–						
	10/52									14.4	4.4	norm.									+	–	–	–	
	4/53									14.9	4.5	norm.							–						
L. S.	5/47	F	44	6 mo.	6 yrs.	–	norm.*	.5→2.4	12	12.9	3.8	macr.	+	+	–	–	–	–							
408519	2/53									13.1	4.0	norm.	+	improved					?+	–	+	–	–	–	
R. S.	3/49	M	52	2 yrs.	3 yrs.	–	meg.	.5→12.2	6	10.5	3.1	macr.	–	–	–	+	–	–	–						
465127	8/49									16.3	5.0	norm.							–	–					
	12/49																		–	–					
	1/53									16.5	5.0	norm.							–		+	+	–	–	
	2/53																		?+	–					
	3/53																		–						
G. S.	5/50	M	75	6 mos.	3 yrs.	–	0	1.5→12.8	7	10.0	2.6	macr.	–	–	–	–	–	–	–	–					
254061	11/52									16.0	4.5	norm.							–	–	+	+	–	–	
H. W.	10/47	F	49	3 yrs.	6 yrs.	–	meg.	1.1→21.7	5	7.6	1.7	macr.	+	+	–	+	–	–		–					
415798	4/48												–	–											
	2/53																				+	–	–	–	
F. W.	7/38	M	46	5 mos.	15 yrs.	–	0	1→14.7	6	10.2	3.7	macr.	–	–	+	–	–	–		–					
201458	12/41									16.0	4.9	norm.							–	–					
	12/42					–				14.7	4.4	norm.							–	–					
	10/50									13.6	4.1	norm.							–	–					
	11/53																		–		+	–	–	+	
P. W.	8/49	F	31	3 yrs.	4 yrs.	–	meg.	1.3→21.4	5	8.4	1.7	macr.	–	–	–	+	–	–	–	–					
426134	9/50									12.9	4.3	norm.							–						
	4/51									13.4	4.2	norm.							–						
	3/52									12.6	3.8	norm.							–						
	2/53																		–	–	+	–	+	–	

* = Patient partially treated before admission
† = Postoperative smear

KEY
+ = Present
– = Absent
0 = No examination

eryth. = Erythrocytic
meg. = Megaloblastic
macr. = Macrocytic
norm. = Normal

diagnosis was well established in all of these patients. This and other pertinent clinical data are summarized in Table 1. The length of treatment ranged from 6 months to 22 years, with an average of 7 years. Routinely, 3 cell collection techniques[29] were used in sequence: Gastric lavage with Ringer's solution, followed by abrasion of the stomach with the antral abrasive balloon, followed by lavage with buffered chymotrypsin. In 18 of the 21 cases this single routine examination yielded cellular material adequate for our purposes. In 2 cases a second study, and in one case a third were necessary. The smears were fixed while wet in ether-alcohol and stained by a modified Papanicolaou technique[29]. The slides were then carefully scanned to insure observation of all cells.

Observations. The majority of gastric columnar cells seen in patients with *treated* pernicious anemia are not unusual; their nuclei are the same as those seen in any normal stomach (Fig. 1) showing some variation in shape, little variation in size, even chromatin distribution and basally located nuclei (Fig. 3). However, all 21 patients comprising this series had a few groups of columnar cells which differed characteristically from the normal. Such cells were not seen in more than 150 other gastric cytologic examinations which included numerous anemias (non-pernicious), histamine refractory achlorhydrias and gastric malignancies. In our experience these characteristic gastric columnar cells are only found in pernicious anemia and we refer to them as "P.A. cells."

These cells are most readily distinguished by their size. They are big. Measurements were carried out on nuclei of "P.A. cells" and normal columnar cells to determine the relative size increase. Whole cells were not measured because of the frequent difficulty in visualizing cytoplasmic outlines, but it is apparent without measurement that the entire "P.A. cell" is enlarged, not just the nucleus. Using an ocular micrometer, the lengths and widths of 725 "P.A. cell" nuclei and 620 normal columnar nuclei (260 of these were in normal cells occurring in 8 pernicious anemia patients) were recorded in arbitrary units. These dimensions were multiplied together to give a function of the area of optical cross-section. The average area for "P.A. cells" was found to be 6.2 units, twice that for normal cells: 3.1 units.

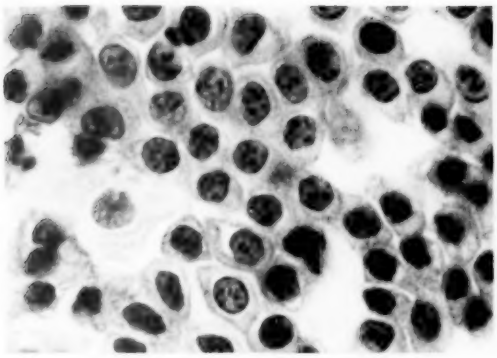
In the cases where controls were drawn from the same patient as the "P.A. cells," the analysis of variants showed that the average difference between the mean sizes of "P.A. cells" and normal cells (548 cells) is 3.1 with a standard error of 0.25.

For the whole series (1,131 cells) including normal control cells from non-pernicious anemias the difference between the mean size of "P.A." and normal cells is also 3.1 units, which is 3 and ½ times the standard deviation (Table 2). This corresponds to a probability of less than 5 parts in 10,000 that the differences occurred by chance.*

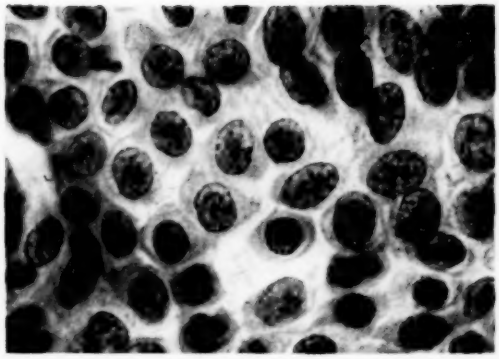
This size difference is well illustrated by Fig. 7 where a group of normal columnar cells is surrounded by "P.A. cells." Figure 11a shows normal and Fig. 11b shows "P.A. cells" also in the same patient.

These cells may have other distinctive morphologic features. Frequently there is a typical creased or folded appearance to the nuclear membrane (Fig. 8). Small aggregates of chromatin stand out on the relatively empty background of the nucleus

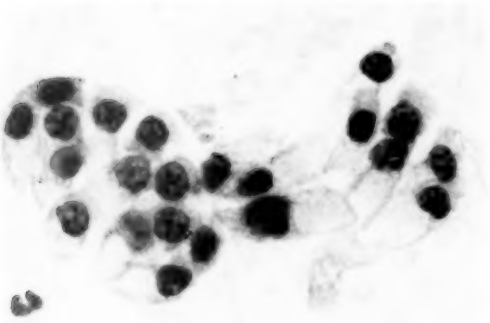
*Mr. Curtis Smith of the Physiology Department, University of Chicago performed this statistical analysis.



1. Normal Columnar Cells—End View—750×

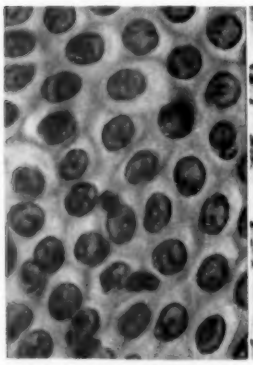


2. Columnar Cells—P.A.—End View—750×

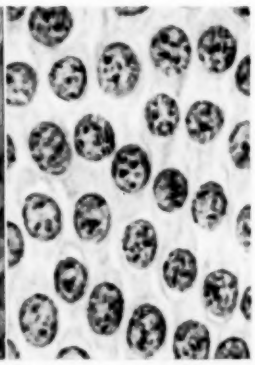


3. Normal Columnar Cells—End and Side View—750×

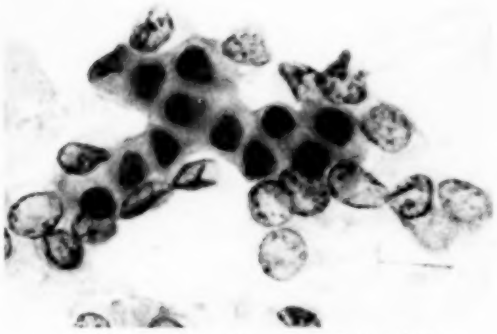
4. Columnar Cells—P.A.—Side View—750×



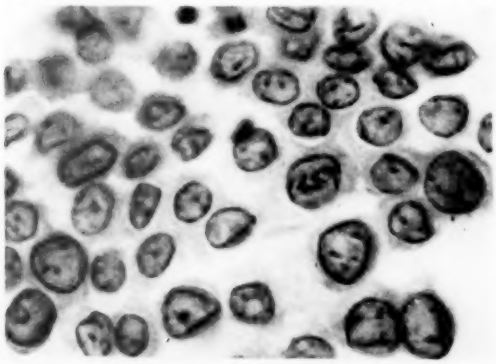
5. Fundal Scraping—P.A.



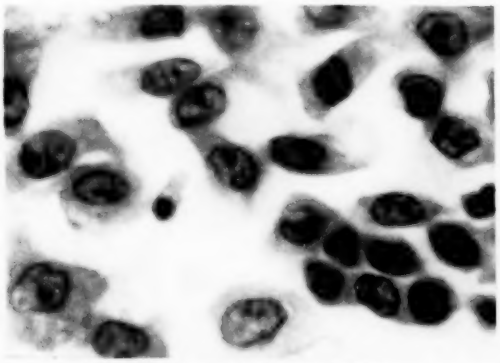
6. Antral Scraping—P.A.



7. Columnar Cells—Normal and P.A.—750×

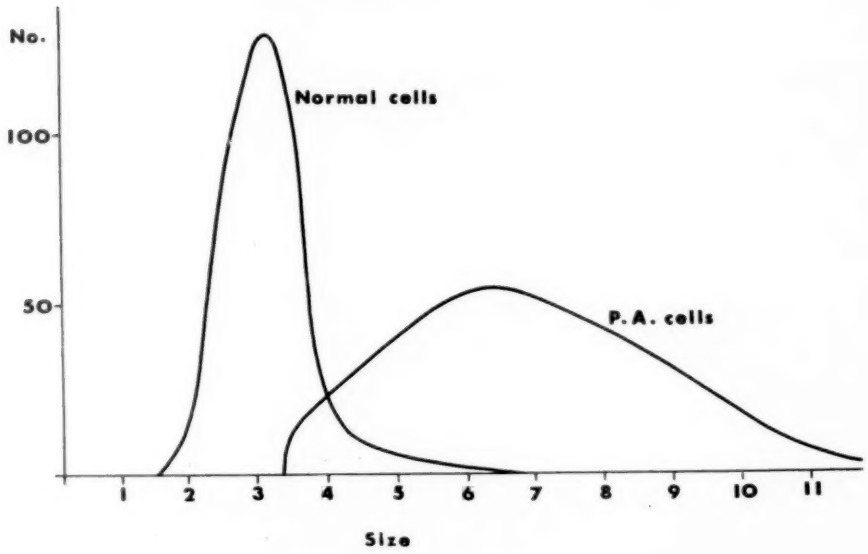


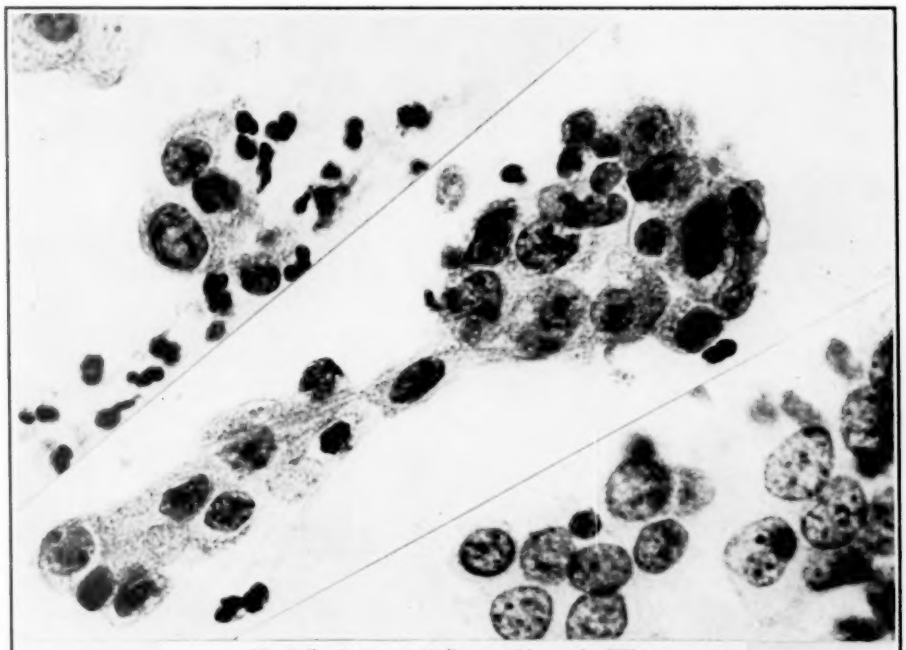
8. P.A.—Bland Cell Type—750×



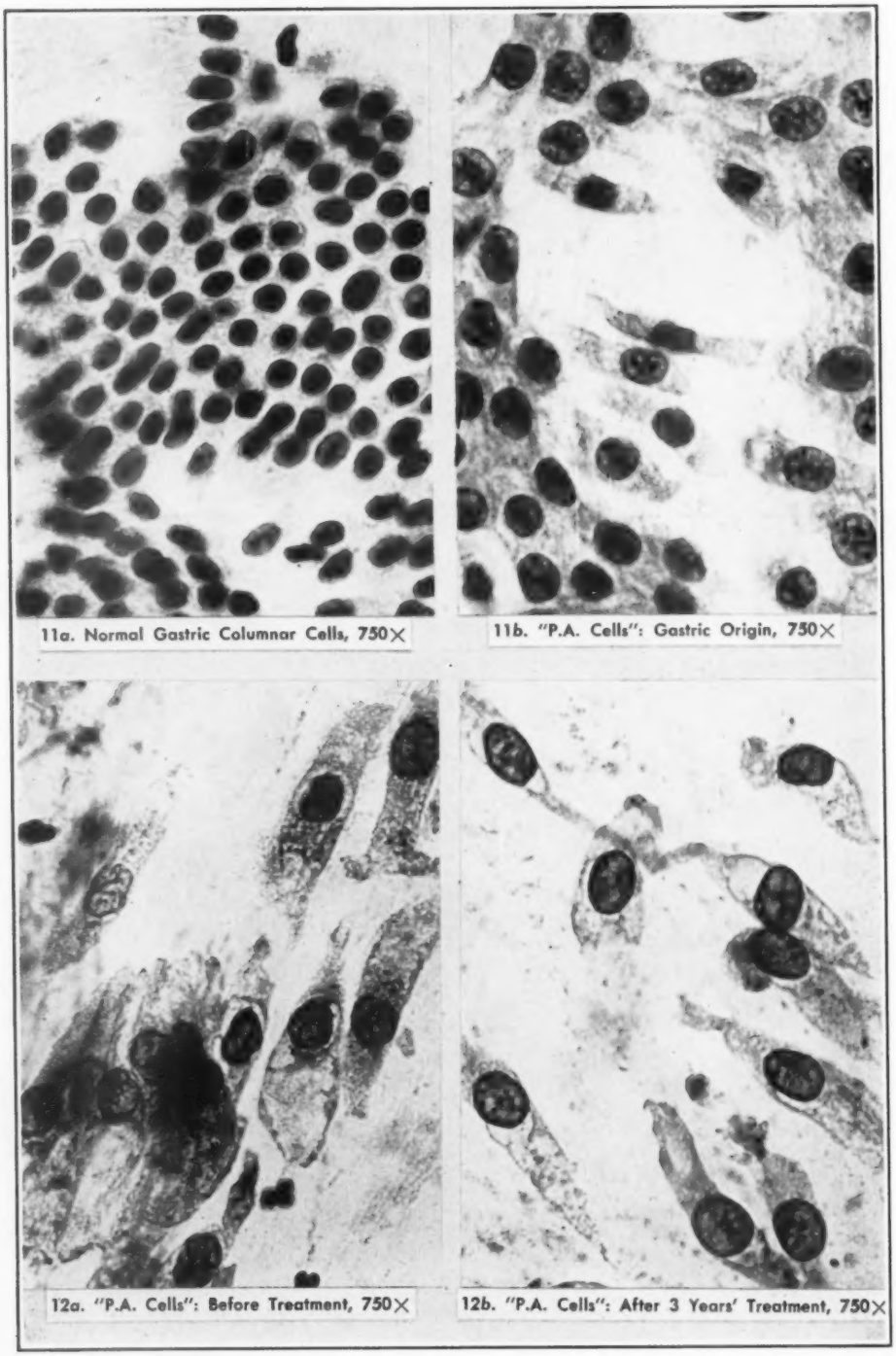
9. P.A.—Active Cell Type—750×

TABLE 2.—DISTRIBUTION OF NUCLEAR SIZES





10. Cells: Incorrect Malignant Diagnosis, 750×



11a. Normal Gastric Columnar Cells, 750×

11b. "P.A. Cells": Gastric Origin, 750×

12a. "P.A. Cells": Before Treatment, 750×

12b. "P.A. Cells": After 3 Years' Treatment, 750×

(Figs. 4, 7, 8). Figure 2 illustrates a less common variant of the "P.A. cell" in which the chromatin is evenly distributed.

The cytoplasm on occasion has a more vacuolated, granular appearance than normal (Fig. 4). Perinuclear halos or half-moon shaped vacuoles may be seen (Figs. 12a and b). These nonspecific cytoplasmic features have also been noted by others[15,17,34].

Large columnar cells closely simulating malignancy were found in several cases which also contained more characteristic "P.A. cells" (Figs. 14a, b and c: same patient). The nuclei were twice normal size, the nuclear membranes irregular in outline, and the nucleoli large, red and refractile (Figs. 9, 13b and c, 14a). The cell outlines may be definitely columnar (Fig. 13c) or at times more squamous in appearance (Fig. 13b). There was, however, no disturbance of the nuclear-cytoplasmic ratio, nor was there the hyperchromatism and marked size variation of the nuclei such as one sees in carcinoma. These are referred to as "active P.A. cells."

After a dozen cases had been examined, the slides on the initial case which had been reported positive were reviewed. In retrospect the cells which were called malignant, now appeared to be "active P.A. cells" and the case was recorded as a reader's error.

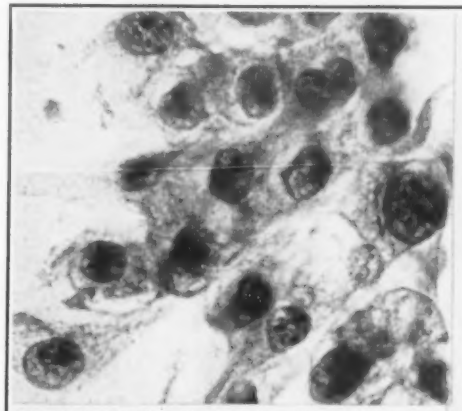
In 3 of the 21 patients repeat cytologic studies were necessary in order to find characteristic "P.A. cells." There is an unpredictable day to day variability in the quality and quantity of all gastric cytologic material. It is therefore not surprising that repeat examinations should be required to find cells which are often conspicuously in the minority. It should be emphasized that three successive examinations may be necessary to establish the presence of "P.A. cells."

Two patients in the series had a subtotal gastrectomy for polyps. Multiple smears were made by scraping the mucosal surface of the freshly resected stomachs, in an attempt to locate the site of origin of the "P.A. cells." No consistent localization was found. In the first case antral scrapings contained cells with some of the characteristics seen in pernicious anemia (Fig. 6), and fundal scrapings were normal (Fig. 5). However, 6 months postoperatively a chymotrypsin lavage of the fundal stump revealed many classical "P.A. cells." In the second case, both antral and fundal scrapings contained cells reminiscent of P.A. Classical "P.A. cells" were present in a chymotrypsin lavage of this fundal stump 3 months after surgery.

Since "P.A. cells" were recovered from both patients after the antrum had been completely removed, it would appear that they may originate in the fundus. Whether they can also exfoliate from the antrum is less clear, for the cytologic morphology of scrapings is not entirely comparable to that of spontaneously exfoliated cells.

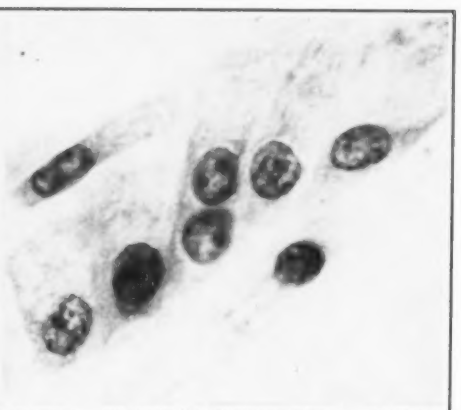
The source of these cells was not apparent in strips of the entire length of the 2 resected stomachs examined histologically by the "Swiss Roll" technique[10]. Nor did careful examination of the polyps reveal cellular changes comparable to those seen in the smears.

Other nonspecific cell types which may also occur in chronic atrophic gastritis were frequently present in these smears. Goblet cells with compressed, basal nuclei and distended, mucus-containing thecae are illustrated in Fig. 15a. This probably reflects intestinalization. Slender, elongated cells with small, centrally-located, pyknotic nuclei were frequently seen (Figs. 16 and 17). These cells resemble respiratory epithelium but their origin from the stomach is suggested by their frequent

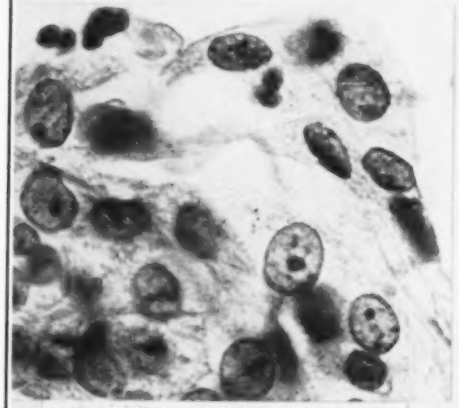


13a. Active "P.A. Cells": Before Treatment, 750×

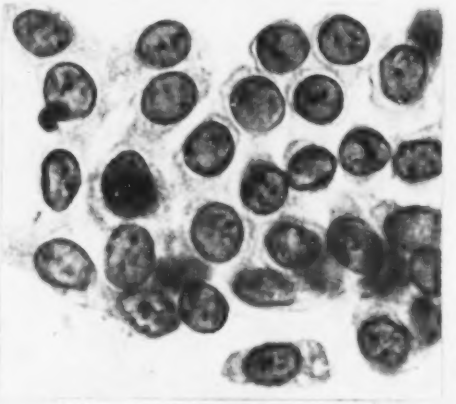
13b. Active "P.A. Cells" 3 Years' Treatment, 750×



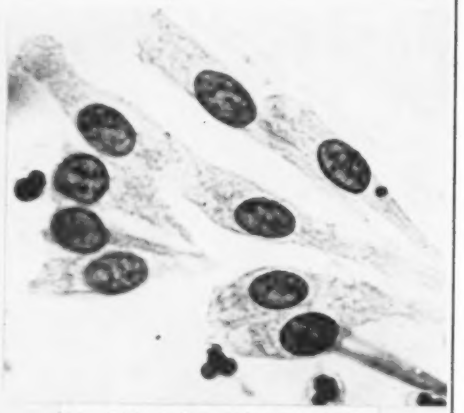
13c. Active "P.A. Cells" 20 Years' Treatment, 750×



14a. Active "P.A. Cells": Syncytium, 750×

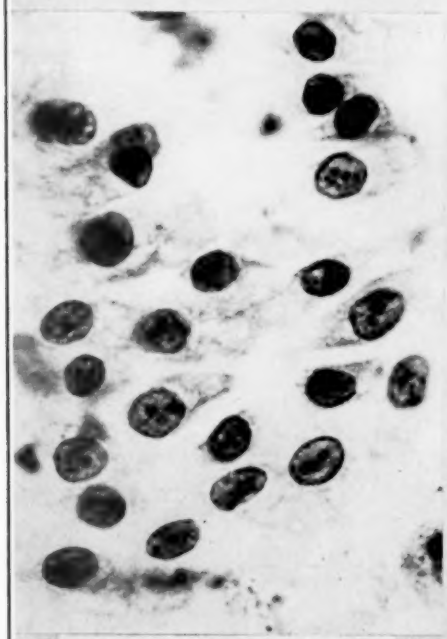


14b. "P.A. Cells": End View, 750×



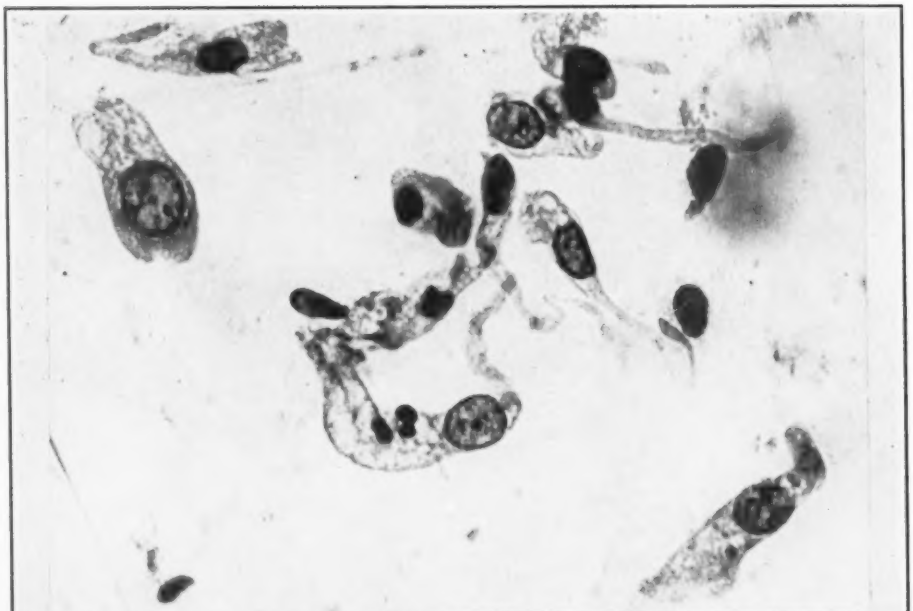
14c. "P.A. Cells": Side View, 750×

15a. Goblet and Slender Cells, 750×



15b. Questionable "P.A. Cells," 750×

15c. "P.A. Cells," 750×



16. Varied Cells: Slender Cells (center); "P.A. Cells" (left upper, lower mid and right lower), 750×

17. Slender Columnar Cells, 750×

occurrence within a group of other types of gastric cells (Figs. 11b, 15a, 16). It is possible that these cells reflect the atrophic process. There is a third heterogeneous group of cells which fall between the normal and the "P.A. cell" in which nuclear enlargement and atypia is variable but not pronounced enough to be characteristic of pernicious anemia. The diversity of cells which may come from the same patient is illustrated in Figs. 14, 15 and 16, each of which represents a single case.

Discussion. Almost a century has passed since Thomas Addison's classic description of pernicious anemia[1]. Fifteen years later Samuel Fenwick in describing the stomach in this disease noted that ". . . the whole of the glandular structure was in a state of atrophy[13]. . . ." In a series of brilliantly conceived and carefully executed experiments, Castle and his colleagues systematically demonstrated a physiologic connection between the gastric defect and this illness[3-9]. It is thus not surprising to find a cytologic clue to the irreversibility of the gastric lesion.

It has been long known that the blood picture in *untreated* pernicious anemia is characterized by large, abnormal cell forms; macrocytes and macropolycytes in the peripheral blood; megaloblasts and large leukocytes in the bone marrow. These changes are not limited to the blood. Henning[17] and Witte[34], using a sponge abrasion technique, obtained some atypical large round cells from the stomachs of 7 patients with pernicious anemia (therapeutic status unreported). Graham and Rheault have recently shown that cells of non-hematopoietic origin from the esophagus, lung, vagina and stomach show macrocytosis and nuclear abnormalities prior to treatment[16]. After specific therapy these cells, like those of the blood, return to normal. This work of Graham and Rheault is further important evidence of the systemic nature of the nutritional deficiency in this disease.

Current studies in our laboratory* on untreated pernicious anemia showed gastric "P.A. cells" (Fig. 12a) indistinguishable from those seen in other cases after years of therapy (Fig. 12b). Both the bland (Fig. 12) and active cell types (Fig. 13) were seen. It should be emphasized again that the "P.A. cells" are usually in the minority, whether the patient has been treated or not. When they appear in large numbers there are always many groups of normal gastric cells to be found in the same smear. The fact that they do not change after treatment is further evidence of the irreversibility of the gastric lesion.

Investigation of a larger series is necessary to determine whether this "P.A. cell" is pathognomonic for the disease. If this proves true then the diagnosis may be established despite the previous institution of specific therapy; a great advantage in these days of shotgun antianemic medication[33]. The latter type of treatment of symptoms may allow combined system disease to pursue its insidious crippling course. Moreover, since the physician is not alerted, the complicating gastric carcinomas of this disease will not be detected in their early stages.

*Dr. Melvin Klayman kindly allowed us to use some of his cytologic data in untreated pernicious anemia.

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REFERENCES

1. **Addison, T.**: On the Constitutional and Local Effects of Disease of the Suprarenal Capsules. London, Highley, 1855.
2. **Brown, M. R.**: New England J. Med., **210**, 473, 1934.
3. **Castle, W. B.**: Am. J. M. Sci., **178**, 748, 1929.
4. Idem: Ann. Int. Med., **34**, 1093, 1951.
5. Idem: New England J. Med., **249**, 603, 1953.
6. **Castle, W. B., Heath, C. W.,** and **Strauss, M. B.**: Am. J. M. Sci., **182**, 741, 1931.
7. **Castle, W. B., Heath, C. W., Strauss, M. B.,** and **Heinle, R. W.**: Ibid., **194**, 618, 1937.
8. **Castle, W. B.,** and **Townsend, W. C.**: Ibid., **178**, 764, 1929.
9. **Castle, W. B., Townsend, W. C.,** and **Heath, C. W.**: Ibid., **180**, 305, 1930.
10. **Cox, A. J.**: Am. J. Path., **19**, 491, 1943.
11. **Doig, R. K.,** and **Wood, I. J.**: Med. J. Australia, **2**, 565, 1950.
12. **Faber, K.,** and **Bloch, C. E.**: Ztschr. klin. Med., **40**, 98, 1900.
13. **Fenwick, S.**: Lancet, **2**, 78, 1870.
14. **Feyrter, F.,** and **Klima, R.**: München med. Wchnschr., **94**, 146, 1952.
15. **Graham, R. M.**: Personal communication.
16. **Graham, R. M.,** and **Rheault, M. H.**: J. Lab. & Clin. Med., in press.
17. **Henning, N.,** and **Witte, S.**: Deutsche med. Wchnschr., **77**, 1, 1952.
18. **Jenner, A. W. F.**: Acta med. scandinav., **102**, 529, 1939.
19. **Jones, F. A.**: Modern Trends in Gastroenterology. New York, Paul B. Hoeber, Inc., 1952, Chapt. 14 by **H. A. Magnus.**
20. **Jorgensen, J.**: Acta med. scandinav., **139**, 472, 1951.
21. **Kaplan, H. S.,** and **Rigler, L. G.**: Am. J. M. Sci., **209**, 339, 1945.
22. **Magnus, H. A.,** and **Unglev, C. C.**: Lancet, **1**, 420, 1938.
23. **Meulengracht, E.**: Am. J. M. Sci., **197**, 201, 1939.
24. **Mosbech, J.,** and **Videback, A.**: Brit. Med. J., **2**, 390, 1950.
25. **Motteram, R.**: J. Path. and Bact., **63**, 389, 1951.
26. **Rambach, H.**: Monatschr. f. Krebsbekämpf., **4**, 201, 1936.
27. **Rigler, J. G.,** and **Kaplan, H. S.**: J. Nat. Cancer Inst., **7**, 327, 1947.
28. **Rubin, C. E.**: Unpublished observations.
29. **Rubin, C. E., Massey, B. W., Kirsner, J. B., Palmer, W. L.,** and **Stonecypher, D. D.**: Gastroenterology, **25**, 119, 1953.
30. **State, D., Gaviser, D., Hubbard, G. B.,** and **Wangensteen, O.**: J. Am. Med. Assn., **142**, 1128, 1950.
31. **Van der Sande, D.**: Nedrl. tijdschr. v. Geneesk., **80**, 4774, 1936.
32. **Wallgren, I.**: Arb. a. d. Path. Inst. zu Helsingfors, **3**, 275, 1925.
33. **Wintrobe, M. M.**: Am. J. Med., **15**, 141, 1953.
34. **Witte, S.**: Verhandl. deutsch. Gesellsch. in. Med., 57 Kongress. München, J. F. Bergman, 1951, pp. 260-262.

AN INVESTIGATION OF SOME PSYCHOLOGICAL EFFECTS ACCOMPANYING ISONIAZID THERAPY ON TUBERCULOUS PATIENTS

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When the early enthusiastic results of the drug, isonicotinic acid hydrazide (Isoniazid or INH) became a matter of public interest, sufficient pressure was brought to bear on physicians to utilize this form of treatment, although complete and adequate research had not been done. Aside from the direct effects of the drug in the treatment of tuberculosis, both concern and interest were raised as to its side effects on the function of the kidneys, liver and blood, and its toxic effects as reflected by mood swings, mild delirium, vasomotor instability, delay in micturition, and others. It has been demonstrated that toxic doses of Isoniazid have produced convulsions in all species of laboratory animals tested[2,11]. One case of an epileptic who died of convulsions while under Isoniazid therapy is reported[4]. Amberson, in reviewing the work of others at the Twelfth Conference on the Chemotherapy of Tuberculosis, Atlanta, Georgia, points out that while drug psychosis may occur, the process can be reversed by discontinuing its use. While these workers have brought out possible deleterious mental effects of the drug and the need for caution in its use, a recent study suggests that the psychological effects of the drug may not be all negative. Kreiser *et al.*[9] administered the drug to a group of tuberculous mental patients. While the primary purpose was to study the effects on tuberculosis, they also reported the side effects on the patients' mental condition. They indicate that 21 of the 48 patients showed either marked (6), moderate (12), or slight (3) improvement. Although no controls were employed, the authors believe that the results are meaningful, since these patients had been given other forms of medical treatment and showed no behavioral improvement. However, they are cautious to indicate that the gains may not necessarily be considered, in all cases, from a social standpoint, but rather in terms relative to the patients' previous condition. The means for evaluating the improvement is thus stated by the authors: "In arriving at the evaluation of the individual patient's mental condition, we accepted the diagnosis as made previously by the psychiatrist and as stated in the patient's record. We should like to stress the point that this was an unexpected and purely casual observation made during a study designed for an entirely different purpose." Thus, neither objective measuring instruments nor criteria for assessing behavioral improvement are offered.

Since the widespread use of INH might be questioned if it were shown to be accompanied by deleterious psychological effects, it is important to determine what psychological changes, if any, accompany the use of INH. It is the purpose of this paper to present a comparison of the results of psychological examinations administered to tuberculous patients prior to the initiation of INH therapy with the results obtained after a minimum period of 6 months. At the time this study was begun in June, 1952, less information

was available about the effects of the drug than the little we now have. The essence of the reports received was that it worked wonders on tuberculosis and that a few deaths and psychoses developed.

If the drug does bring about psychological changes, what is their nature? Would there be changes in basic personality structure, personality traits, memory, or motor functions? Each of these aspects of personality was considered to be possibly susceptible to the influence of INH and was examined. The general hypothesis, which will be rendered specific for each of the tested variables, is that patients under INH therapy for a period of 6 months or more will not show adverse psychological effects.

Procedure. SAMPLE. The subjects of this study were male, veteran tuberculous patients at the Veterans Administration Hospital, Butler, Pa. They were selected at random on the basis of their register number at the time of admission to the hospital. In order to maintain consistent procedure, all patients, prior to the administration of the psychological examination, were informed that they were to receive Isoniazid shortly. After a minimum period of 6 months on INH therapy, psychological examinations were readministered. Due to a variety of factors the number of patients retested is approximately 25 to 50% less, depending upon the particular test used, than the number tested prior to receiving INH. The factors which prevented the maintenance of the complete sample are as follows:

1. Patients being discharged with maximum hospital benefits before completion of 6 months on INH.

2. Patients being discharged against medical advice or who were absent without leave prior to completion of 6 months on INH.

3. Patients refusing to take a second examination.

4. Patients unable to be retested because of medical reasons.

5. Patients having to be eliminated because of the introduction of psychotherapy.

6. Patients having test results which were invalid.

7. Patients dying prior to completion of 6 months on INH therapy. It might be of interest to note that none of the sample was lost due to discontinuation of the drug.

Since a considerable proportion of the sample could not be retested, due principally to rejection of both hospital treatment and re-examination, some question might be raised as to whether selective factors were operating which caused some patients to sustain hospitalization and accept re-examination, and other patients to reject hospitalization and refuse re-examination. To test this hypothesis, a comparison was made between the group that offered no resistance (Cooperative) with that which offered resistance (Uncooperative) by means of the initial scores obtained on the Minnesota Multiphasic Personality Inventory (MMPI) and the Scale of Inner Maladjustment (SIM) based on the MMPI. As can be noted in Table 1, no statistically significant differences were found between the scores obtained by the two groups. Since the group eliminated from the study did not differ significantly from the group remaining, the sample tested can be considered to be representative of the hospital population.

The over-all age range of the patients was from 21 to 74 years. The average age and age range for the number of patients taking the particular tests are given in Table 2.

CONTROL. Since the problem in this study was to determine whether patients under INH therapy would show

adverse psychological effects, a comparison of their test results before and after the administration of INH would provide an answer. Thus, in regard to the question of controls, the first test will serve as a standard or control against which the results of the second test can be evaluated.

It was also considered at the outset to set up a control group against which the direction and magnitude of the changes, if any, in the INH group could be compared. Such a control group would consist of patients whose sole treatment would be bed rest. Practically, this could not be accomplished since every patient was given some form of therapy over and above bed rest. In fact, since very few of the patients were on any other treatment but INH, or combination of INH and streptomycin, at the time this study was to begin, the only group that could be used for comparative purposes was one consisting of 17 patients treated with streptomycin. Obviously, this is not an ideal control group, especially since the psychological effects of streptomycin on patients has not been subject to test. Nevertheless, streptomycin is an accepted form of treatment and the question of its adverse psychological effects has not been a matter of concern to physicians. Thus, it was believed that some value could be obtained by comparing the results of this group with the INH group. The 17 patients on streptomycin were, therefore, given MMPI's under conditions similar to those of patients on INH. Two of the cases were eliminated because of invalid records, so that the final group consisted of 15 cases. The average age of this group was 33.1 years with an age range of 22 to 43 years. Comparison groups of this sort were not obtained for other tests.

TABLE 1.—A COMPARISON OF THE INITIAL MMPI AND SIM SCORES OF COOPERATIVE AND UNCOOPERATIVE PATIENTS

	Mean Score of Group That Was:		*Mean Difference*	
	Uncooperative	*Cooperative*	(M_{UNCO}–M_{CO})	*t-score*
Hypochondriasis	67.37	71.02	−3.65	.911
Depression	70.47	68.36	2.11	.703
Hysteria	63.47	64.67	−1.20	.407
Psychopathic Deviate	63.42	62.69	0.73	.238
Masculinity-Femininity	52.58	53.47	−0.89	.378
Paranoid	49.89	49.09	0.80	.321
Psychasthenia	60.05	58.58	1.47	.472
Schizophrenia	58.63	54.02	4.61	1.804
Hypomania	60.95	56.31	4.64	1.784
Scale of Inner Maladjustment	31.89	26.78	5.11	1.394

TABLE 2.—THE NUMBER, MEAN AGE, AND AGE RANGE OF PATIENTS USED ON EACH TEST

Test	*Number*	*Average Age*	*Age Range*
MMPI	45	35.3	21 to 57
Bell Adjustment Inventory	28	38.7	24 to 74
GAMIN	27	36.5	22 to 61
STDCR	25	36.4	22 to 61
Rorschach	21	38.7	24 to 74
Wechsler-Memory	24	36.7	22 to 60
Digit Symbol	9	40.0	23 to 61

INSTRUMENTS. Since we were interested in exploring possible areas of psychological changes, it was decided to utilize psychological instruments that would measure a variety of personality

characteristics. The instruments used and the means for evaluating these instruments are offered below.

Measure of Basic Personality Structure: Rorschach. The Rorschach was administered and scored in accordance with Klopfer's system[8]. A measure of adjustment was obtained by employing a system devised by Davidson[3]. This system is based on 17 signs of adjustment which are likely to appear in a record. Three judges rated the examinations. There was very high agreement among the raters on most of the signs. Signs of color shock and shading shock offered much disagreement and were, therefore, eliminated from the final scores. On the remaining few points of disagreement, the three judges discussed their differences of opinion and arrived at a decision. Thus, the ultimate ratings of the 15 signs represent 100% agreement of the judges. The presence of more or less signs in the second Rorschach than in the first was taken as a tendency towards better or worse basic adjustment, respectively.

Measures of Personality Traits, Factors, and Characteristics. MMPI. Since the items on the scales utilized are included within the first 366 items, only these were answered. Responses to additional items beyond 366 which appear on the K scale, were also required. The appropriate proportion of the K score was added to the respective scales and the test was scored according to standard procedures[7]. The raw scores were converted to T-scores which were utilized in the analysis. Higher scores on second administration were taken as a tendency towards maladjustment, while lower scores were taken as a trend towards better adjustment with regard to the particular variable measure.

An additional scale known as the Scale of Inner Maladjustment (SIM) developed previously by the writer and modified for this study, was also utilized[12]. This modification was necesitated by the fact that the original scale of 170 items was based on the 565 items in the MMPI booklet. Since only 366 items plus the K items were used, the form of the Scale of Inner Maladjustment based on these items only contained 135 items. The number of items selected on the first and second administrations were compared. Higher and lower scores made on the second administration were taken as indications of worse or better inner adjustment, respectively.

Bell Adjustment Inventory: Adult Form. This test was administered and scored in the standard manner[1]. While the inventory provides 5 separate measures of personal and social adjustment, namely, Home, Occupational, Health, Social, and Emotional adjustment, only the last three measures were considered to be important and applicable to the population employed. This is obvious when it is understood that these patients have been unemployed and away from home for considerable periods of time. Rather than call undue attention to the significant items, the whole test was administered. Increased scale scores on second administration were taken to indicate poor adjustment in the particular area affected, while the reverse held for decreases.

STDCR and GAMIN. Since there is a marked similarity in the development, administration, and scoring of both of these tests, they will be considered together. Each test, representing five independent personality traits, was administered and scored according to standard procedures[5,6]. Higher scores on second administration was taken as more socially desirable while the opposite held for lower scores.

Measure of Memory Function: Wechsler Memory Scale. This test was used in order to compare various as-

pects of memory function before and after INH therapy. In order to reduce any practice or memory effects, Form I was administered before INH therapy and Form II was given after 6 months. The first two sections of the test (I, Personal and Current Information, and II, Orientation) did not seem appropriate for our population and, therefore, were not used. The remaining 5 sections were given and scored in accordance with standard procedures[13]. Increased raw scores on the particular sections were indicative of increased memory function.

or non-independent, measures, the statistical procedure most appropriate to test the significance of the difference between the means of these scores is the following one offered by Lindquist[10]:

$$t = \frac{M_o - M_h}{\sqrt{\frac{d^2}{n(n-1)}}}$$

In essence, it will be determined whether the observed difference between the means (M_o or $M_1 - M_2$) of the two administrations differs signifi-

TABLE 3.—THE MEAN DIFFERENCES, SIGNIFICANCE TESTS, AND PSYCHOLOGICAL TRENDS OBTAINED BY COMPARING THE INITIAL AND SECOND MMPI AND SIM SCORES FOR BOTH THE INH AND STREPTOMYCIN GROUPS AND BETWEEN THESE TWO GROUPS

MMPI	*INH Group (N=45)*			*Streptomycin Group (N=15)*			*INH vs Streptomycin*	
		Psychological			*Psychological*		$(M_1-M_2)_{INH}-(M_1-M_2)_{SM}$	
Scale	M_1-M_2	*Trend*	t_{INH}	M_1-M_2	*Trend*	t_{SM}		t_{INH-SM}
Hs	−0.36	−	0.218	−1.93	−	0.555	1.90	0.543
D	1.84	+	1.264	−1.20	−	0.385	3.04	0.983
Hy	−1.16	−	0.761	−1.00	−	0.463	−0.16	0.053
Pd	0.56	+	0.367	−1.33	−	0.677	0.78	0.271
Mf	−0.76	−	0.629	1.93	+	1.017	−2.69	1.143
Pa	−1.69	−	1.218	0.93	+	0.415	−2.62	0.960
Pt	1.40	+	0.878	−3.27	−	1.080	4.87	1.430
Sc	−2.04	−	1.426	−3.93	−	1.348	1.89	.631
Ma	−2.40	−	1.643	1.07	+	0.373	−3.47	1.148
SIM	3.07	+	2.541**	−0.33	−	0.098	−3.40	1.193

**Significant at the .05 level of confidence

Measure of Motor Function: Digit Symbol. The digit symbol test was used principally because of its emphasis on a combination of motor control and speed. Forms I and II of the Wechsler Bellevue Intelligence Scale were employed[14]. The procedure for the tests was similar in that the subjects were given 90 seconds on each performance. Increase or decrease in the number of symbols completed indicate a corresponding increase or decrease in motor control.

Results. Since the scores obtained on the first and second tests are related, cantly from a hypothetical mean of zero (M_h).

The differences obtained between the means of the two administrations (M_1-M_2) and the tests of significance are offered in Tables 3 and 4. Since the meaning of the changes that might occur after the second administration depends upon the particular test employed a category called Psychological Trends has been included in the tables to signify the positive and negative psychological effects.

MMPI. As can be seen in Table 3, none of the 9 MMPI scales show any

statistically significant differences between the first and second tests of patients on INH therapy. The SIM Scale does show a statistically significant decrease, indicating a decrease in feelings of inner maladjustment. The group of patients on streptomycin therapy similarly show no statistically significant difference on MMPI Scales as well as the SIM Scale between the two administrations of the tests. A comparison of the mean differences between the INH and streptomycin group in the MMPI and SIM Scales reveals no statistically significant differences. These results are reported in Table 3.

Table 4 contains the results of the remaining tests administered. The reader is asked to refer to this table for specific mean differences between first and second administration of the tests, the psychological trends, as well as for the results of the tests of significance.

TABLE 4.—THE MEAN DIFFERENCES, SIGNIFICANCE TESTS AND PSYCHOLOGICAL TRENDS OBTAINED BY COMPARING THE RESULTS OF PSYCHOLOGICAL TESTS ADMINISTERED TO PATIENTS PRIOR TO, AND A MINIMUM OF 6 MONTHS AFTER INH THERAPY

Psychological Test	$M_1 - M_2$	*Psychological Trend*	t_{12}
Rorschach	−0.71	+	1.433
Bell Adjustment Inventory:			
Social Adjustment	3.23	+	3.940°°
Emotional Adjustment	1.50	+	1.730
Health Adjustment	0.54	+	0.959
Home Adjustment	−0.27	−	0.034
Occupational Adjustment	0.42	+	0.578
Total Adjustment	5.42	+	2.265°
Subtotal (Social, Emotional, Health)	5.27	+	3.780°°
STDCR:			
S—Social Introversion-Extraversion	−0.60	+	0.540
T—Thinking Introversion-Extroversion	3.28	−	1.590
D—Depression	1.12	−	0.503
C—Cycloid Disposition	1.08	−	0.523
R—Rhathymia	−1.72	+	1.000
GAMIN:			
G—Pressure for Overt Activity	−1.07	+	1.532
A—Ascendency in Social Situations	0.30	−	0.440
M—Masculine Attitudes	−0.74	+	0.815
I —Self-confidence	0.96	−	0.744
N—Lack of Nervous Tenseness	0.33	−	0.250
Wechsler-Memory Scale:			
Mental Control	−0.71	+	1.513
Logical Memory	0.31	−	0.741
Digit Span	−0.13	+	0.371
Visual Reproduction	−2.71	+	3.863°
Associate Learning	0.21	−	0.305
Total	−3.00	+	2.318
Digit Symbol	−2.33	+	1.000

°Significant at the .01 level of confidence
°°Significant at the .05 level of confidence

Rorschach. A tendency toward better basic adjustment is indicated on the Rorschach by the .71 average increase in number of adjustment signs and the fact that 10 of 21 patients showed higher scores on the second test, with only 4 showing lower scores and 7 showing no change. However, this tendency is not of sufficient magnitude to yield a statistically significant difference as indicated by the t-score of 1.433.

Bell Adjustment Inventory. It will be recalled that the scales of Home and Occupational adjustment were not considered appropriate for use with this population. While their results are presented, in addition to the other three scales and the total adjustment score for the sake of completeness, a subgroup score based only on the three appropriate scales (Health, Social, and Emotional) was also computed. It will be seen in Table 4 that each of these scales, except for Home, reveal tendencies toward better adjustment with the social scale and subgroup, showing statistically significant differences indicative of better adjustment. Even with the inclusion of the Home and Occupational scales, the mean difference between the total adjustment scores is seen to be statistically significant in favor of positive adjustment.

STDCR and GAMIN. Of the 10 factors on the STDCR and GAMIN, 6 show negative trends, while 4 show positive trends. None of these factors reveals any differences between the first and second administrations that could not be accounted for by chance.

Wechsler-Memory Scale. Of the 5 individual subtests employed on the Wechsler-Memory Scale, 2 show negligible decreases while 3 show increases, ranging from 2 negligible increases to one statistically significant increase. This latter result, which occurs on the subtest, Visual Reproduction, pertains to an increased ability to reproduce visual designs from memory. A comparison of the totals of the 5 subtests of the 2 administrations reveals statistically significant differences in favor of the second performance over the first.

Digit Symbol. While 6 of 9 subjects obtained higher scores on the second administration of the digit symbol test than on the first, the resulting tests of significance reveal no statistically significant difference between the two separate scores.

Discussion. The general hypothesis as stated earlier, that patients under Isoniazid therapy will not show accompanying adverse psychological effects, is borne out by each of the factors tested. In the absence of more adequate controls and in the presence of several statistically significant positive effects, it might be wondered what the results would have been if proper control could have been employed. The fact that statistically significant positive results were obtained on the Scale of Inner Maladjustment for the INH groups, while similar results were not obtained on this scale for the streptomycin group, does not permit us to draw any conclusions as to the drug's absolute effects. It is possible that if each of the results obtained could have been compared with those of a control group having no chemotherapy, the differences between the two groups might have been increased, decreased, or remained the same. It is also important to note that, although the average increase in the INH group on the SIM Scale is greater than that obtained on the streptomycin group, this difference between the 2 groups was not found to be statistically significant. These points are being emphasized as a means of caution against the possible interpretation that the drug will produce positive psychological effects. If, however, we adhere

strictly to a comparison of the results of the first and second administrations, which is our major concern, it would seem reasonable to expect no serious psychological effects accompanying the use of INH on groups of patients. It must be borne in mind that the results are based on groups (and small groups at that) and that individual variations tend to be submerged when the data are grouped. While no analysis of individual records was made for formal presentation, each of the tests was carefully examined for the specific purpose of informing the physician of any marked psychological deviation. In only one case (involving a patient who took the Rorschach) was the discrepancy between the two tests of any concern, the second being markedly poorer. Whether or not this is an indirect result of INH therapy is open to serious question. The patient was called to the psychologist's attention on several occasions prior to the initiation of INH therapy because he appeared depressed. He had periodic mood swings and at the time of retest was sufficiently in the throes of depression for his physician to refer him for psychotherapy. There is no doubt that his attitude at the time of testing affected the results. It is the opinion of the writer, however, that the poorer performance on retest was not the result of psychological changes induced by INH, but due rather to other unspecified factors that caused the re-arousal of emotional problems that had plagued him over many years. This opinion is supported by the fact that shortly after the referral and prior to contact with a psychologist this patient's physician reported that his current behavior did not warrant psychological referral. While the patient was disturbed, it was never of an acute or sufficient degree to consider or warrant the discontinuation of INH therapy.

An interesting aspect of the study, and one worthy of some future investigation, was that certain measures provided statistically significant positive results. In addition to this factor, one might also speculate on the meaning of the generally more positive results obtained, which include some statistically significant results, on measures dealing principally with adjustment factors, for example, the Scale of Inner Maladjustment, Bell Adjustment Inventory, and Rorschach Test, as compared with measures dealing principally with personality factors; STDCR and GAMIN or diagnostic categories; MMPI (this is not to be taken to mean that the STDCR and GAMIN, and MMPI do not reveal important aspects of personality from which adjustment can be inferred, but rather that they do not provide specific or direct measures of adjustment). It is possible that the positive therapeutic effects of INH on tuberculosis give rise to feelings of well-being which are thus reflected in the psychological test performance. Perhaps, this feeling of well-being is also responsible for the statistically significant positive results obtained on the Wechsler Memory Scale and the subtest Visual Reproduction. If such an explanation were valid, it might well be asked why significant findings were not obtained for other measures. Since 3 of the 5 subtests of the Wechsler Memory Scale show positive results, it is obvious that there is no consistent tendency towards better memory function as suggested by the statistically significant difference between the totals of the 2 forms of the test. This difference is accounted for principally by the marked increase in the second performance of the subtest, Visual Reproduction over the first. It is possible that Form II of this test provides a less demanding performance than Form I. However, it is the writer's

opinion that such is not the case. In any event, it would not appear reasonable to make a general statement about increased memory function in spite of the statistically significant difference, but rather that there seems to be an increased ability to reproduce designs from memory. More important, however, is that the decrease that occurs on some of the subtests are negligible, indicating that memory function in general does not show adverse effects in patients under INH therapy.

In essence, what has been said about memory function applies to the other psychological variables. Some measures show negative tendencies, others positive. Some of the latter are statistically significant. However, the important question as to whether or not INH therapy will be accompanied by adverse psychological effects, either directly or indirectly, has been answered within the limitations of this study in the negative, in accordance with the general hypothesis stated and the specific hypotheses tested.

Summary and Conclusions. A variety of psychological tests including measures of basic personality structure, personality traits and characteristics, in addition to tests of memory and motor functions were administered to groups of tuberculous patients, prior to and 6 months after the administration of Isoniazid therapy, for the purpose of determining whether adverse psychological effects accompanied the use of the drug.

The tests used included the Rorschach, Minnesota Multiphasic Personality Inventory, Scale of Inner Maladjustment, Bell Adjustment Inventory, STDCR and GAMIN, Wechsler-Memory Scale, Digit Symbol.

The t-test was the statistical procedure used to test the significance of differences of the means obtained between the first and second administrations.

A group of patients on streptomycin therapy were used for comparative purposes on the MMPI. A comparison of the results of the streptomycin group with that of the INH group on the MMPI and Scale of Inner Maladjustment yields no statistically significant differences.

Statistically significant positive results were found on the following tests: Scale of Inner Maladjustment, Bell Adjustment Inventory; Total, Subtotal (Social, Health, Emotional), and Social, Wechsler-Memory; Total and Visual Reproduction. No statistically significant negative results were found.

The possibility of positive adjustment tendencies accompanying the use of the drug is considered. Most essential is that the results of the study bear out the general hypothesis that patients under Isoniazid therapy do not show deleterious psychological effects.

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REFERENCES

1. **Bell, H. M.:** Manual for the Adjustment Inventory: Adult Form. Stanford University, Calif., Stanford University Press.
2. **Benson, W. M., Stefko, P. L.,** and **Roe, M. D.:** Am. Rev. Tuberc., **65,** 376, 1952.
3. **Davidson, H. H.:** J. Proj. Tech., **14,** 31, 1950.
4. **Fetterhoff, K. I., Holmes, C. X.,** and **Martin, G. E.:** Am. Rev. Tuberc., **66,** 501, 1952.

5. **Guilford, J. P.:** Manual for the Inventory of Factors STDCR. Beverly Hills, Calif., Sheridan Supply Co.
6. **Guilford, J. P.,** and **Martin, H. G.:** Manual for the Inventory of Factors GAMIN. Beverly Hills, Calif., Sheridan Supply Co.
7. **Hathaway, S. R.,** and **McKinley, J. C.:** Manual for the Minnesota Multiphasic Personality Inventory. New York, Psychological Corporation, 1951.
8. **Klopfer, B.:** The Rorschach Technique. Yonkers, New York, World Book Company, 1946.
9. **Kreiser, A. E., Sanderson, A., Vik, M.,** and **Myers, J. A.:** Dis. Chest, **23,** 28, 1953.
10. **Lindquist, E. F.:** Statistical Analysis in Educational Research. Cambridge, Mass., Houghton Mifflin Co., 1940.
11. **Rubin, B., Hassert, G. L., Thomas, B. G. H.,** and **Burke, J. C.:** Am. Rev. Tuberc., **65,** 392, 1952.
12. **Simon, R.:** An Investigation of the Relationship Between Several Measures of Self-Insight and Adjustment, Intelligence and Personality Characteristics, Unpublished Ph.D. dissertation, Syracuse University, 1952.
13. **Wechsler, D.:** Manual for the Wechsler-Memory Scale. New York, Psychological Corporation, 1945.
14. Idem: The Measurement of Adult Intelligence. Baltimore, Williams & Wilkins Co., 1944.

LOW DIASTOLIC PRESSURE AS A CLINICAL FEATURE OF RHEUMATOID ARTHRITIS AND ITS POSSIBLE ETIOLOGIC SIGNIFICANCE

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Although students of the rheumatic diseases are aware that blood pressure tends to be low in cases of rheumatoid arthritis, we have been unable to find any reference to a specific study of this relationship. The observations of blood pressure readings in 320 unselected cases of rheumatoid arthritis here reported indicate that arterial hypotension is so constant a finding that it may be regarded as an integral feature of the disease. The interest in these findings is heightened by recent reports[3,6,9] that the hypotensive agents Apresoline (1-hydrazinophthalazine) and hexamethonium are capable of inducing syndromes which closely resemble three connective tissue diseases: rheumatoid arthritis, disseminated lupus erythematosus and scleroderma.

Methods and Materials. The charts of 320 cases of rheumatoid arthritis admitted to Temple University Hospital or to the Arthritis Clinic over the last decade were reviewed. In all cases the arthritis had been present for a minimum of 9 months and the diagnosis was certified by a senior member of the arthritis clinic. The admission blood pressure was selected so as to avoid any possible hypotensive effect of bed rest.

The figures for "normal" blood pressure readings, by decades, are available from the reports of a number of previous studies. In Table 1 and Fig. 1, we have used the average blood pressure of 5540 (male and female) patients as given by Bordley and Eichna[1], based on their analysis of Weatherby's figures. Their study seemed to offer the least selected and therefore the most suitable group for comparison. (Slightly lower figures were reported by Hunter[5] and considerably higher figures for normal are suggested by Master, Garfield and Walters[7].)

Conversely our search among over 100 hypertensive patients disclosed no cases of typical rheumatoid arthritis. However, since the incidence of rheumatoid arthritis in the general population is probably much less than 1 per cent, several thousand hypertensives would have to be surveyed in order to obtain a statistically significant figure as to the incidence of rheumatoid arthritis among them.

Results. These are summarized in Table 1 and Fig. 1. It is immediately apparent that the average blood pressure, by decades, in the arthritis group is strikingly different from that of the control group. The average diastolic blood pressure of the arthritics remains essentially unchanged for all decades at a level of about 75 of mercury, whereas the average of diastolic pressures for controls rises with each decade. The difference between the average systolic blood pressures for both groups is definite, although not so striking.

An analysis of individual blood pressures among the group of 320 rheumatoid arthritics reveals a total of 14 patients whose pressure would be class-

ed as hypertensive. Their average blood pressure was 156/91 and their average age was 59. We were not able in this study to be sure of the etiology of their hypertension. Several were obviously suffering from atherosclerosis and in one case the hypertension was apparently secondary to an old toxemia of pregnancy.

Comment. CLINICAL APPLICATION.

TABLE 1.—AVERAGE BLOOD PRESSURE FIGURES IN NORMALS AND IN PATIENTS WITH RHEUMATOID ARTHRITIS

Ages by decades	*No. of Arthritic patients*	*Average B.P. of arthritic patients*	*Average B.P. of 5540 non-arthritics*
20-29	29	115/74	120/77
30-39	68	113/73	124/80
40-49	82	118/74	133/84
50-59	86	127/77	145/87
60-69	39	131/73	155/91
70-	16	127/75	166/92

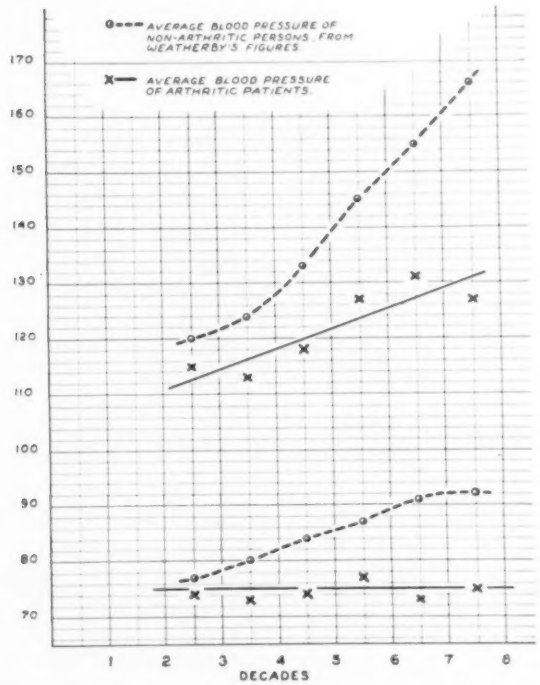

Fig. 1.—Graph of Blood Pressure Data in Normals and in Patients with Rheumatoid Arthritis.

From a practical, clinical point of view the above study indicates two points of interest:

1. Diastolic hypotension would seem to be a quite constant feature of rheumatoid arthritis and, when found, may thus add appreciable weight to the differential diagnosis of the arthritides.
2. The incidence of hypertension in cases of true rheumatoid arthritis is so rare (about 5% in our series) that a patient with both arthritis and hypertension should perhaps be suspected of having gout, osteoarthritis, chronic infectious arthritis, or some other non-rheumatoid form of arthritis. (This agrees well with the necropsy findings in a series of 101 cases of rheumatoid arthritis reported by Cobb, Anderson and Bauer[2] in which hypertensive heart disease was reported in only 2% of cases.)

ETIOLOGIC IMPLICATIONS. In considering the possible significance of this diastolic hypotension in the pathogenesis of rheumatoid arthritis, some interesting possibilities come to mind.

First of all, it may of course have no special significance at all. It may be merely a reflection of general debility, as it appears to be in several other unrelated diseases. While a few of our patients were febrile this does not appear to be sufficient to be an important factor in causing hypotension.

However, a careful appraisal of the emotional patterns in our cases of rheumatoid arthritis indicates that, in the great majority of our cases either an acute or chronic emotional stress precedes the onset of the disease, and exacerbates it once it is established. Likewise, in chronic essential hypertension, emotional stress unquestionably plays a major precipitating and sustaining role. We are therefore faced with two diametrically opposed effects on blood pressure which occur in response to apparently similar, if not identical, kinds of emotional stress.

What determines which of these two dissimilar vascular responses will occur in any given case?

Factors to be considered are such things as possible anatomical differences in the nervous system associated with body type, or perhaps differences in basically conditional reflexes which may in some way determine the avenues for the discharge of energy over the efferent nervous pathways in response to severe emotional stress.

With this last thought in mind, the action of Apresoline in blocking the energy discharges over certain autonomic pathways is of the greatest interest, since a prolonged blockade, sufficient to normalize the diastolic blood pressure, precipitates in about 7.5% of cases clinical syndromes closely resembling rheumatoid arthritis, disseminated lupus and possibly scleroderma. Not only the articular manifestations, but deviations in the sedimentation rate, serum proteins, and others parallel the laboratory abnormalities found in these diseases, as will be noted from the following brief résumé of recent reports by 3 groups of investigators.

Dustan *et al.*[3] describe a "rheumatic and febrile syndrome" occurring during prolonged hydralazine therapy in hypertensive patients. The syndrome occurred in 13 of a series of 139 patients most of whom had attained an excellent hypotensive response after receiving large (average 640 mg. daily) doses of Apresoline. After receiving this drug for an average period of 12 months, the 13 patients suffered a migratory arthralgia most frequently involving the proximal interphalangeal joints. The affected joints were stiff, tender, warm and reddened, with fusiform swelling resembling that of rheu-

matoid arthritis. Other features of rheumatoid arthritis, such as increased sedimentation rate, decrease in serum albumin and increase in alpha and gamma globulins, anemia, leukopenia, and biopsy evidence of muscle lymphorrhagia, were also observed. The signs and symptoms were suppressed by ACTH and cortisone therapy. The syndrome subsided in an average of one week on withdrawing the drug, but recurred in the majority of cases on readministration of Apresoline.

In 5 of the 13 patients who continued to take the drug despite the onset of rheumatic symptoms a "febrile phase" resembling acute disseminated lupus erythematosus was observed. In these cases, various combinations of fever, prostration, pericardial and pleural effusions, pneumonitis, erythemas and further lowering of blood pressure occurred. The syndrome differed from acute disseminated lupus in that the L-E cell was generally absent, 4 of the 5 patients were males and proteinuria and cylinduria were not increased.

Lindauer and Hafkenschiel[6] observed an essentially similar syndrome in 16 of 175 hypertensive patients on long-term Apresoline therapy. Positive serologic tests for syphilis were noted in 4 cases and a positive L-E cell test occurred in one case in which the full clinical picture of acute disseminated lupus erythematosus, including the characteristic butterfly rash, was present. Most of the affected patients were also taking hexamethonium and veratrum preparations.

Morrow, Schroeder and Perry[9] report almost identical findings in 14 of 253 patients receiving combined Apresoline and hexamethonium therapy. They also observed microscopic hematuria, anemia, splenomegaly and lymphadenopathy. All cases showing these "rheumatic" effects had an exaggerated hypotensive effect with diastolic blood pressure at 90 mm. Hg. In addition, these authors noted 5 deaths in patients with malignant hypertension receiving Apresoline and hexamethonium therapy due to an acute interstitial fibrosis of the lungs. The syndrome came on suddenly with increasing dyspnea and proved fatal in about one month. Necropsy studies revealed an acute interstitial fibrosis of the lungs which was histologically identical with the rare spontaneous syndrome described by Hamman and Rich[4] under the name of Acute Diffuse Interstitial Fibrosis of the Lungs. Fourteen cases of this syndrome were collected and analyzed in 1952 by Rubin *et al.*[10], the cardinal clinical features being increasing dyspnea not increased by recumbency, cyanosis, cough, fever and chest pain. Death occurs from suffocation or cardiac failure. The main objective findings are Roentgen evidence for diffuse bilateral pulmonary infiltrations with patchy consolidations, and cardiac enlargement. The etiology of this syndrome is unknown. Histologically it resembles the pulmonary findings of scleroderma. Clinically it suggests a progressive and irreversible phase of the transient pulmonary infiltrations which may complicate almost all the dyscollagenoses. Morrow *et al.* cite a report by Morrison[8] of apparently similar pulmonary lesions occurring during treatment of a hypertensive patient by hexamethonium alone. They infer that hexamethonium rather than Apresoline may be the causal agent in their fatal cases of pulmonary fibrosis.

In this brief review of the syndromes induced by hypotensive agents we see the nearest approach as yet attained to the experimental production of rheumatoid arthritis, disseminated lupus erythematosus and possibly of scleroderma in man. The high incidence (a total of 43 out of 567 cases receiving long-term Apresoline or hexamethon-

ium therapy or both) of these "rheumatic" reactions and the large number of points in which they closely resemble the spontaneously occurring collagen diseases indicate that they are of a different order from the mere arthralgias which may be precipitated by other drugs such as sulfonamides or iodides. That the effect is due to hypersensitivity also seems unlikely, since the syndrome is not invariably evoked by readministration of Apresoline; also, it occasionally persists after withdrawal of the drug. It appears that the rheumatoid and lupoid effects are due to Apresoline alone and that the pulmonary lesions are caused by hexamethonium. The mode of action in both instances may of course be a direct chemical effect at the tissue level. However it seems not improbable that the hypotensive action of both these drugs may be a clue to their dyscollagenotic action. In the case of Apresoline, Morrow *et al.*[9] stress the fact that collagen disease appears only in those cases with normal or nearly normalized blood pressure. Muscle aches have also been noted as a side effect of the hypotensive drug "Serpasil": an alkaloid of *Rauwolfia serpentina*.

The fact that 3 chemically unrelated hypotensive drugs may precipitate "rheumatic" syndromes strengthens the hypothesis that these effects are in some way related to the lowering of blood pressure.

While these drug-induced syndromes are not identical with the naturally occurring diseases, the resemblance is sufficiently striking to suggest at least that a common mechanism is operating at some unknown level in both instances. Such a close parallelism can hardly be due to chance.

The hypothesis that a diversion of the efferent neural discharges is a possible clue to the nature of the disturbed physiology in both the drug-induced and naturally occurring syndromes is not in any sense here offered as a full explanation of the pathogenesis of the connective tissue diseases under consideration, but rather as a possible explanation of the mode of action of the precipitating and exacerbating factors in their etiology: a tentative hypothesis, to be confirmed or denied by future investigation.

Summary. Blood pressure readings in 320 unselected cases of rheumatoid arthritis reveal an average diastolic hypotension of about 75 mm. Hg for all decades. This is so constant (95% of cases) that it constitutes a clinical feature of the disease and may therefore be of value in the differential diagnosis of the arthritides.

Both rheumatoid arthritis and essential hypertension may be precipitated and exacerbated by emotional stress, although they are otherwise largely mutually exclusive diseases.

Blockade of efferent neural discharges by Apresoline, or hexamethonium, or both, in hypertensives causes a series of syndromes closely resembling rheumatoid arthritis, disseminated lupus erythematosus and possibly scleroderma.

The authors postulate that the precipitating factor in these diseases may therefore be a hypothalmic disturbance resulting in abnormal efferent neural discharges, and that in hypertensive cases the drug induced autonomic blockade may divert this energy into those pathways which result in the production of the collagen diseases instead of hypertension.

REFERENCES

1. **Bordley, J., III,** and **Eichna, L. W.:** Internat. Clin., **48,** 175, 1938.
2. **Cobb, S., Anderson, F.,** and **Bauer, W.:** New England J. Med., **249,** 553, 1953.

3. **Dustan, H. P., Taylor, R. D., Corcoran, A. C.,** and **Page, I. H.**: J. Am. Med. Assn., **154**, 23, 1954.
4. **Hamman, L.,** and **Rich, A.**: Bull. Johns Hopkins Hosp., **74**, 177, 1944.
5. **Hunter, A.**: Proc. Assn. Life Ins. Pres., **8**, 27, 1914.
6. **Lindauer, M. A.,** and **Hafkenschiel, J. H.**: Paper presented at the Section on General Medicine, College of Physicians of Philadelphia, November 23, 1953.
7. **Master, A. M., Garfield, C. I.,** and **Walters, M. B.**: Normal Blood Pressure and Hypertension, Philadelphia, Lea & Febiger, 1952.
8. **Morrison, B.**: Brit. Med. J., **1**, 1291, 1953.
9. **Morrow, I. D., Schroeder, H. A.,** and **Perry, H. M., Jr.**: Circulation, **8**, 829, 1953.
10. **Rubin, E. H., Kahn, B. S.,** and **Pecker, D.**: Ann. Int. Med., **36**, 827, 1952.

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BODY POSITION IN RELATION TO VENOUS AIR EMBOLISM: A ROENTGENOLOGIC STUDY*

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Reports of death due to venous air embolism continue to appear in medical literature[14]. There is good reason to believe, furthermore, that those instances which are reported constitute only a relatively small proportion of the actual number of accidents of this type[11]. Failure to diagnose air embolism may be responsible for some of this disparity, but in many instances the physician, for various reasons, does not report the accident. The authors have been much impressed by the considerable number of incidents reported to them by personal communication since their interest has become generally known. It would appear that the subject has far greater importance than has been appreciated, and it is one that must be understood by physicians in all branches of medical endeavor, since the likelihood of its occurrence is not limited to one, or even a few, specialties. It is quite evident from a survey of the literature that any procedure, diagnostic or therapeutic, which allows a venous channel to be exposed to gas under pressure greater than that of its blood column may permit embolization to occur. Whether or not the result will be a serious one depends upon a number of factors, including the amount and kind of gas which gains entrance, the pressure of the gas, the position of the patient, and the efficiency of the cardio-pulmonary apparatus. Many physicians have, no doubt, been lulled into a false sense of security by recalling the difficulty experienced in their student days killing laboratory animals by air injections. It should be clearly understood that relatively small amounts of air (probably as little as 40 cc.) can be fatal to persons who are not in good health. Furthermore, all physicians should have a

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general knowledge of the basic circulatory and respiratory pathophysiology so that effective therapy may be employed when, and if, an accident does occur.

In previous communications[7,12] we have presented evidence demonstrating the favorable effect of the left lateral position in venous air embolism. We showed that the mortality rate in dogs injected with 7.5 cc. of air per kg. was almost twice as high when the animals were supine as when they were on their left sides at the time of the air injection[12]. The favorable influence of the left lateral position held true also when the animals were turned from the back to the left side within one minute after the injection. Our studies concerning the mechanism involved in this favorable effect suggested that the left lateral position allowed the displacement of an air trap from the outflow tract of the right ventricle, permitting circulation of blood to continue while the gas is being disposed of gradually by the lungs.

The present extension of our investigations was made possible by the development of a biplane stereoscopic angiocardiographic device by Dr. W. E. Chamberlain and coworkers[3,4]. This device permitted an investigation into some aspects of air behavior in the cardio-pulmonary circulation not possible by any other means.

Method. The biplane stereoscopic angiocardiograph used in this study consists of 2 Fairchild roll film magazines mounted at right angles to each other in a large circular frame with 2 radiographic tubes, one of these being opposite to each of the roll film magazines. Each of the latter takes 75 feet of 9-inch wide roll film, and exposures approximately 9 inches square are made at the approximate rate of one every 0.7 second on each magazine, the film therein being advanced between intensifying fluorescent screens. Crank shaft mechanisms driven by a synchronous motor provide side to side displacement of each of the Roentgen tubes between exposures, so that each image on the two sets of film at right angles to each other is stereoscopic with the image before it and following it on the roll. The electrical connection of the 2 Roentgen tubes is such that they fire simultaneously. Their stereoscopic shift is timed to occur while the film is advancing between the intensifying screens.

Ten dogs were used for these experiments. Identification of structures seen by the roentgenogram was aided by stainless steel markers placed chronically around the pulmonary artery, or by catheters introduced into the pulmonary artery via the great veins and right heart, by postmortem correlation, and by a recently reported study of the Roentgen anatomy of the dog's heart[13]. The anesthesia used and the methods for recording circulatory and respiratory responses were similar to those described previously[12]. Four of the animals were in the dorsal recumbent and 6 in the left lateral position throughout the experiment. A dose of 7.5 cc. of air/kg. of body weight was injected into the femoral vein in all of the animals. Biplane Roentgen exposures were made at frequent intervals and correlated with the circulatory and respiratory records. Necropsy examination was performed on all animals, the location of any residual air being carefully determined.

Results. LEFT LATERAL POSITION. Of the 6 animals studied in this position 4 survived, one died after a delay, and the sixth died shortly after the air injection. This survival rate agrees well with that previously reported (63% in a much larger series of animals[12]). As in previously reported studies, the systemic blood pressure fell abruptly following the injection of air in all of these animals (Fig. 1). Coincident with the development of hypotension there was a marked decrease in pulmonary artery Roentgen density, indicating the presence of air in this vessel. In the 4 animals which recovered there was either a fluctuating or progressive decrease in the amount of pulmonary artery air during the hypotensive period until evidences of recovery became apparent. This was true also of the animal which succumbed 11 minutes after being apparently on the road to recovery. In the sixth ani-

mal the roentgenologic evidence of considerable amounts of air in this artery persisted until the death of the animal. The disappearance of the air from the pulmonary artery in the surviving animals occurred either coincident with or within a period of 30 seconds prior to the rise in systemic blood pressure which heralded recovery (at 8 minutes in Fig. 1, represented also by Fig. 4C). The respiratory records demonstrated alternating bouts of polypnea and apnea, as previously described[12], and it was noted that the presence of this respiratory arrhythmia coincided with the period when there was evidence of air in the pulmonary artery (Fig. 1). It is important to note that there was little or no coincident change in whole blood carbon dioxide or oxygen contents, indicating that anoxia and hypercapnia were not factors in the results obtained.

Right ventricular and right auricular densities were also markedly altered during the course of the embolization. Both chambers showed a marked decrease in density, but, when there was a difference, the lessening of density was more marked in the right atrium than in the ventricle. There was often a reciprocal relationship between the densities in the right heart and those in the pulmonary artery. As the density in the pulmonary artery decreased, signifying more air and less blood in this location, the density in the right heart tended to increase (more blood, less air). This indicated the pumping of air from the heart into the pulmonary artery. On the other hand, when the pulmonary artery density increased (more blood, less air), the right heart density tended to decrease (more air, less blood). The decreased density in the right heart under these circumstances could be explained either by the return of air from the pulmonary artery to the right ventricle by the principle of air buoyancy, or it could represent the delivery of more air from the venæ cavæ to the heart. At necropsy the survivors had no air in the heart or great vessels 20 to 30 minutes after the injection. In the fatal cases there was air in the right heart, in the pulmonary artery and its branches, and in the venæ cavæ.

SUPINE POSITION. Only one of the 4 animals studied in this position survived. The 3 fatal cases all showed air in the right heart and pulmonary artery within a remarkably short time after the injection (it made its appearance within these structures in the second of the first stereo pair of films made at the time of the injection: hence after an interval of only 0.7 second). The amount of air remained constant or actually increased throughout the period of observation. The systemic blood pressure fell abruptly and remained low, and respiration passed quickly through a hyperpneic phase into persistent apnea. The hepatic vessels, venæ cavæ, and pulmonary artery showed persistent filling with air.

The surviving supine animal did not show air in the heart until 75 seconds after the injection. We have no explanation for this unusual delay. There were only traces of air in the pulmonary artery until 9 minutes after the injection when considerable amounts briefly appeared within it and then disappeared. The right atrium and ventricle contained large amounts of air from 75 seconds until 6 minutes, at which time there began a gradual lessening, progressing to total disappearance over a period of 3 minutes. It is of great interest that this animal, which showed so little air in the pulmonary artery during the greater part of the experiment, had no period of apnea. There occurred, however, a persistent polypnea from 125 seconds after the injection until the last observation

at 12 minutes. The blood pressure began to rise at 125 seconds and rapidly reached control levels which were maintained to the end of the experiment.

VISUALIZATION OF CARDIOVASCULAR STRUCTURES. The serial biplane roentgenograms made possible excellent visualization of the right heart chambers and right ventricular outflow tract. It was possible to visualize fluid levels within these structures whenever both air and blood were present simultaneously, and when the beam was directed in the plane of the blood-air interface. Thus, when the animal was in the supine position a fluid level was noted in the lateral projection (Fig. 2B), but when the animal was in the left lateral position it was seen in the posteroanterior projection (Fig. 3A). Whenever the beam was at right angles to the blood-air interface (as in the posteroanterior projection with the animal supine, or the lateral projection with the animal on his left side) no fluid level was seen (Figs. 2A and 3B respectively), but there was a lessening of density over the air-containing portion of the heart, due to the traversing by the beam of blood and air in series. The outline of the air bubble could often be well seen, however (Fig. 2A). It was frequently possible to obtain excellent visualization of the internal anatomy of the dog's heart in many of the films. In the lateral projection, with the animals in the supine position, a portion of the tricuspid ring could be well seen, and it was often possible to visualize the pulmonary valve, as well as the trabeculations on the endocardial surface of the right ventricle (Fig. 2B). The dense shadow of the left ventricle was well visualized through the aerated right ventricle. In the lateral projections of the animals lying on the left side, the venæ cavæ, the right auricle, and the tricuspid ring were often well seen (Fig. 3B).

The posteroanterior projections of animals in the left side down position (Fig. 3A) showed the air within the right ventricle to be trapped *away from* the right ventricular outflow tract, with the blood layer lying in relationship to this tract and favoring continuation of blood flow to the lungs. This is in contrast to the result in the supine position, since, in it, the outflow tract was filled with air, and the blood level was mainly limited to the right atrium and inflow tract of right ventricle, well away from the pulmonary artery, thus favoring the pumping of air rather than blood into the lungs (Fig. 2B). While it is true that the left lateral position favored continuation of circulation of blood to the lungs because of the trapping of air away from the outflow tract, this position did not prevent the eventual expulsion of the air from the ventricular cavity. This is seen in the selected sequence from one of the experiments (Fig. 4A–C). In Fig. 4B, the air previously present within the right auricle and ventricle (Fig. 4A) has been expelled, and the only remaining air is a bubble located in the right branch of the pulmonary artery. The subsequent film (Fig. 4C) shows even this bubble to have disappeared. The eventual removal of gas from the right ventricle in the left lateral position, in defiance of the principle of air buoyancy, is evidently accomplished by maintenance of vigorous ventricular contractions and by the aspirating effect of deep inspiration.

In some of the experiments excellent visualization of the hepatic veins was achieved (Fig. 2A and Fig. 5). This was best seen in the lateral projection with the animal supine (Fig. 5). Attempts to accomplish this same visualization alone by means of air injected through a catheter into the hepatic vein

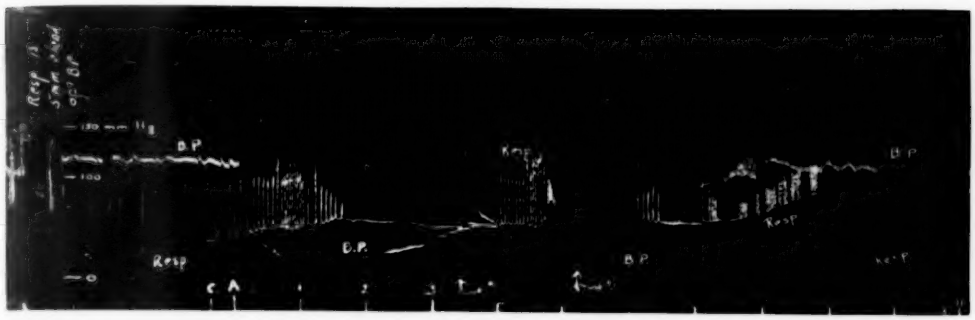


Fig. 1.—Dog #CD, 13.6 kg. Pentothal-barbital anesthesia. At the left margin the arterial blood pressure (B.P., mercury manometer) is above and respiration (Resp., spirometer) is below. The calibration for blood pressure in mm. of Hg is at the left margin. At the bottom of the record, C = control condition, A = air injection. The numbers represent time in minutes. The roentgenograms reproduced in Figs. 4A, B and C are from this same experiment and the time of exposure may be identified on this record by noting that they were taken at 15 seconds, 4 minutes, and 8 minutes respectively.

The extremely long period of hypotension (6 minutes) prior to recovery should be noted. The characteristic preliminary hyperpnea and bouts of dyspnea punctuating the long apnea are readily seen in this record. At 8 minutes, when the pulmonary artery is free of air (Fig. 4C), the blood pressure and respiration are restored to normal.

A

B

Fig. 2A.—Postero-anterior projection, animal on back. Two minutes, 10 seconds after air injection. The wire ring previously inserted in the pulmonary artery is seen just to the left of the spine. The nearly circular shadow of lessened density within the lower central portion of the cardiac outline, which represents the air bubble in the right atrium and ventricle, is well seen. The density of the non-air-containing left ventricle borders this shadow on the left. The air-filled hepatic veins are seen within the density of the liver shadow.

Fig. 2B.—Lateral view, animal on back, two minutes after air injection. Fluid level readily seen in right atrium and inferior portion of right ventricle. The density of the blood-containing left ventricle is seen through the air-distended right chambers. The tricuspid ring is represented as a curved line extending ventrally and cephalad from the fluid level. The right ventricular outflow tract curves cephalad and dorsad from the body of the right ventricle, and, as it nears the superimposed right atrial fluid level, a cusp of the pulmonary valve is seen.

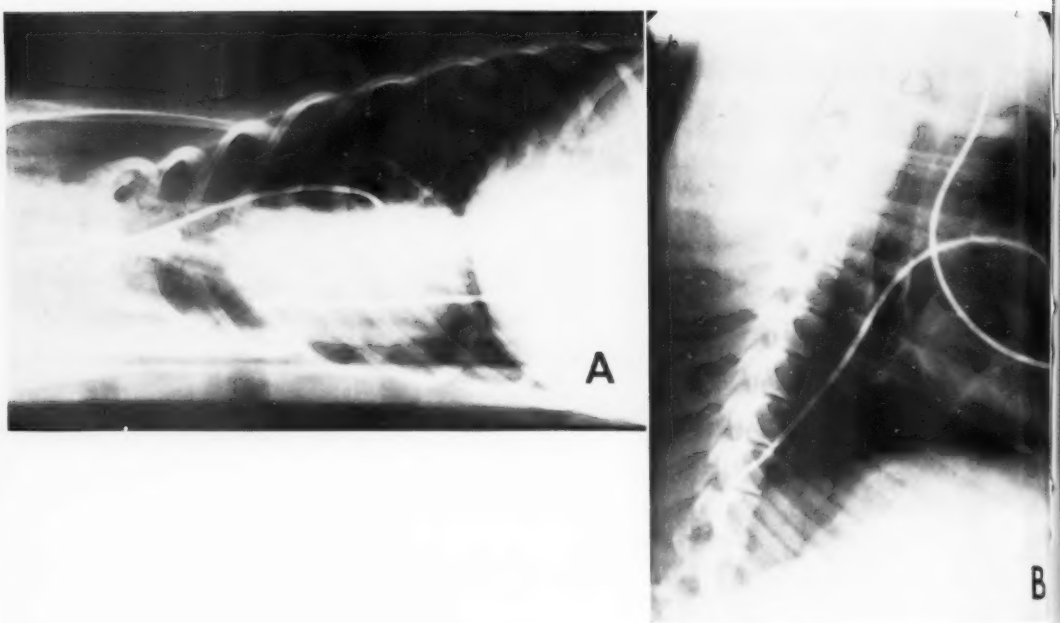
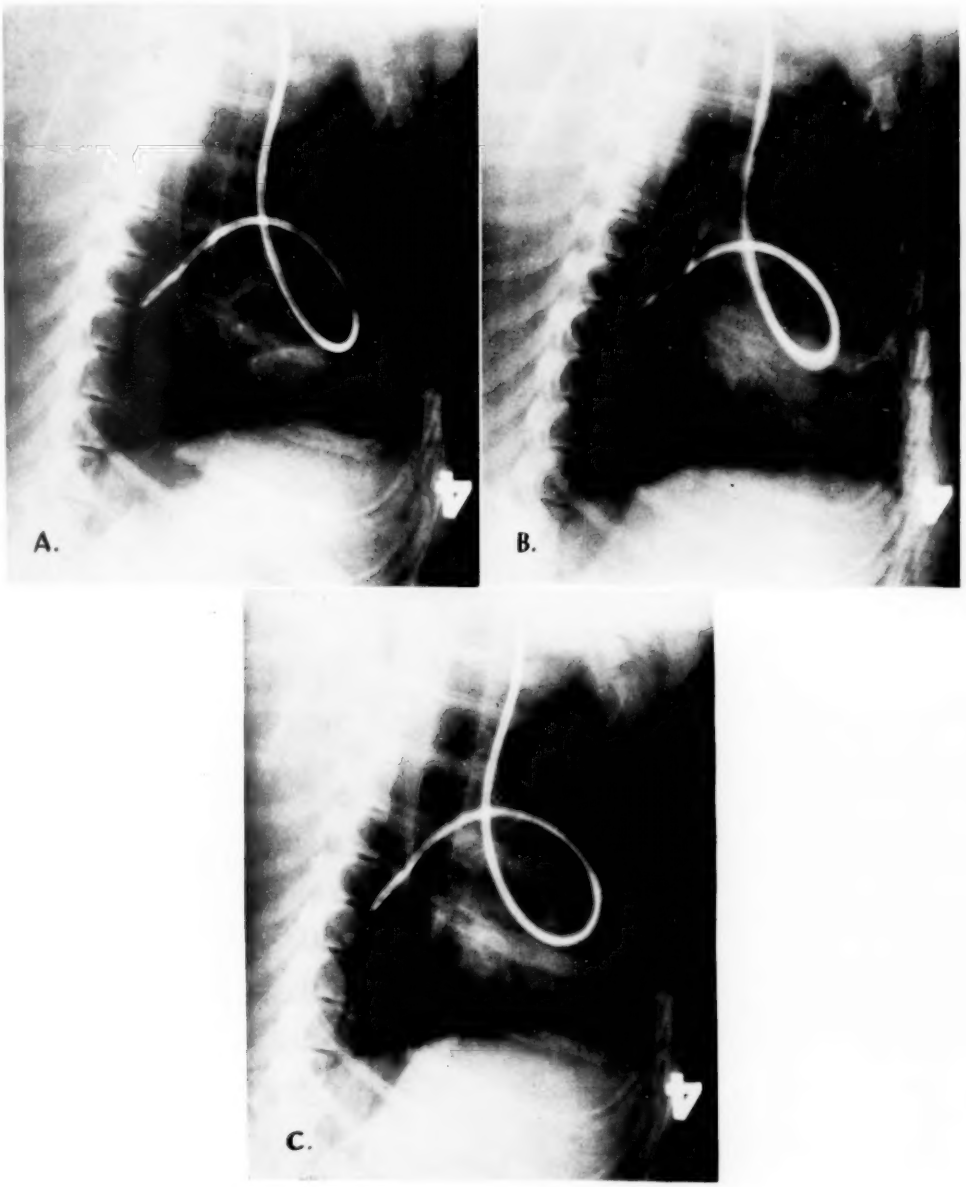


Fig. 3A.—Postero-anterior projection, animal on left side, two minutes after air injection. A catheter is seen passing through the right atrium, into the right ventricle, thence turning to pass through the right ventricle and pulmonary valve, and bending once more as it enters the left pulmonary artery to pass on to the base of the left lung. The fluid level in the right atrium and ventricle is well shown. The shadow of the wall of the right ventricle is seen to be thicker than that of the right atrium. It should be noted that continuity of blood flow from the cavæ to the right ventricular outflow tract is not interrupted by the air trap.

Fig. 3B.—Lateral projection, animal on left side, two minutes after air injection. The catheter is again visualized. No fluid level is seen since the Roentgen beam traverses the air bubble and then the blood, and is not at right angles to their interface. The air-containing inferior vena cava is seen entering the postero-inferior aspect of the heart shadow. The air-containing right atrium accounts for the area of lessened density in the superior portion of the heart, and beneath it passes the right ventricular outflow tract containing the catheter. The tricuspid ring is seen between the area of lessened density and the right atrium and that of the right ventricle.

were unsuccessful, since the injected air was washed out of the liver immediately by the large flow of hepatic blood. Attempts are being made, however, to accomplish this by means of a double-lumen catheter with attached balloon for obstruction of the hepatic vein proximal to the site of air injection.

Discussion. These biplane angiocardiographic studies have demonstrated a number of facts concerning venous air embolism. First, they have shown that air injected into the femoral vein of normal animals usually reaches the right heart almost instantaneously. This is in keeping with the previous observation that the characteristic millwheel murmur, indicative of air and blood being churned within the cardiac chambers, is heard almost immediately after the injection of air. Secondly, they have shown that the presence of



Figs. 4A, B, C.—Representative serial lateral projections taken at 15 seconds, 4 minutes and 8 minutes after air injection respectively with animal on left side. In the first of these the findings are the same as in Fig. 3B. The second shows a disappearance of the air shadow from the right heart chambers, but there is a bubble in the right main branch of the pulmonary artery (the catheter passes into the left branch). The third shows a complete disappearance of all the air. Compare Fig. 1, same animal.

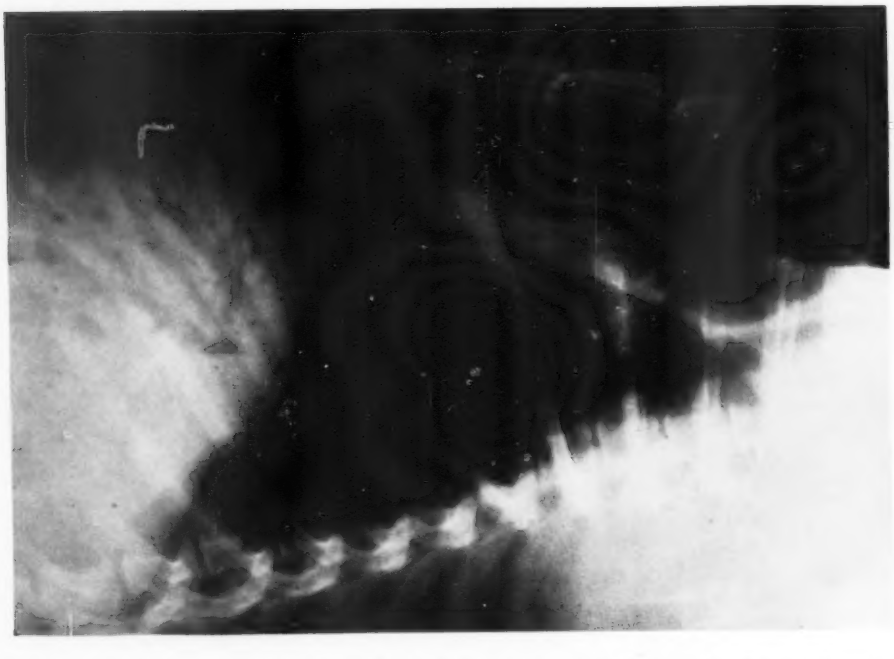
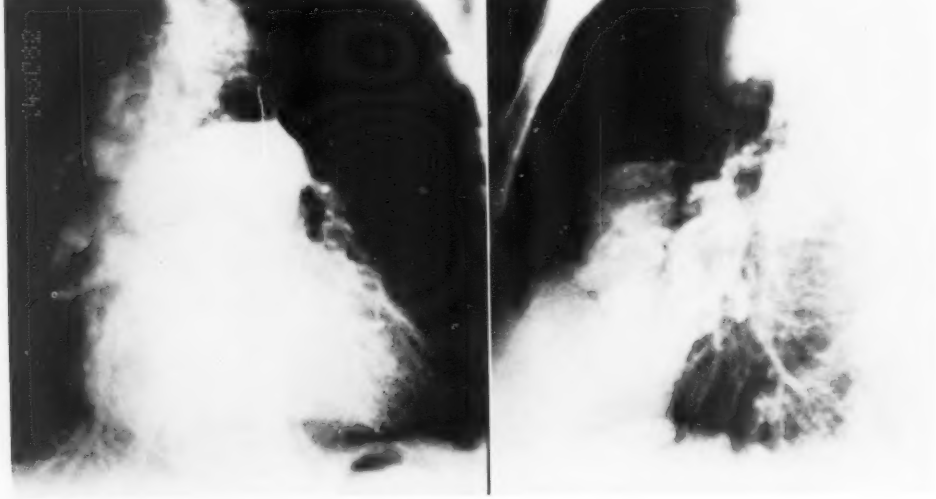


Fig. 5.—Lateral projection, animal on back. Two minutes and 15 seconds after air injection. This view shows the fluid level in the right heart, but it is a particularly good representation of a venohepatogram. The fluid level in the inferior vena cava at the junction of the hepatic veins with this vessel is well seen. The veins themselves with their tributaries are also readily apparent because of their air content.



A B

Figs. 6A and 6B.—Postero-anterior and lateral projections of human Diodrast angiocardiogram, complicated by air embolism. The patient was in the upright position, and the air bubble can be seen, contrasting with the Diodrast shadow, and located in the pulmonary artery and its left main branch.

air in the pulmonary artery is coincident with the systemic hypotension of venous air embolism and also with the characteristic disturbances of respiratory rhythm (Fig. 1 at 4 minutes and Fig. 4B). Thirdly, they have demonstrated the frequent existence of a reciprocal relationship between the amount of air in the pulmonary artery and in the right heart chambers, in animals in the left lateral position. This relationship would appear to result from delivery of air from ventricle into pulmonary artery, or the reverse, by the air buoyancy principle. Fourthly, they have provided further confirmation of the important role played by body position in the mechanisms which determine the likelihood of recovery or death. In this is involved the principle of air buoyancy, air tending to collect in those parts of the circulatory apparatus which are most superiorly located. In the case of animals in the supine position this means that the air, if sufficient in amount, collects in the right heart in such a manner as to result in a severe or complete interruption of the normally continuous column of blood from the cavæ to the pulmonary circulation. This bubble of gas may be thought of as a very effective air trap which, if not displaced, results in circulatory failure and death. In the left lateral position, the air collects in the portion of the right heart *away from* its outflow tract. This does not interrupt the column of blood from the cavæ to the pulmonary artery unless such large amounts of air are injected as to fill the entire right heart. When air does enter the pulmonary circulation in this position, it enters chiefly or only the right pulmonary artery, since this is superiorly located. There is thus little or no impedance to flow of blood through the left lung. It is understandable, then, why there should be a highly significant difference in the comparative mortality rates of these 2 positions when amounts of air approximating the usual lethal dose are injected.

We feel that the results of these studies, together with those that have been reported previously[12], make possible the elucidation of a fairly complete picture concerning the pathophysiology of venous air embolism. When *small amounts* of air are injected into a systemic vein they are carried to the pulmonary arterial circulation, producing temporarily a degree of obstruction which leads to pulmonary arterial hypertension and to certain reflex phenomena. The latter involve the production of systemic hypotension, real and apparent bradycardia, and disturbances of respiratory rhythm. They are akin to the pressoreceptor[1] and von Bezold reflexes[2]. Recovery generally takes place by means of solution, utilization and pulmonary excretion of the air. When larger amounts of air are injected, the same sequence of events is precipitated, but there is now an amount in excess of the elimination capacity and this accumulates within the cavæ, cavities of the right heart and pulmonary vessels. Here the factors outlined in the previous paragraph come into play, involving the amount of air injected and the relative position of the heart chambers and pulmonary circulation. With unfavorable circumstances, the difficulty under which the right heart labors is enhanced by the existence of an unfavorable gradient of coronary flow. The latter is determined, on the one hand, by a fall in the aortic filling pressure, and, on the other, by a rise in the pressure within the chambers to which coronary venous blood is returned. Under favorable circumstances of dose and position, circulation can be maintained by the right heart until all of the air is eliminated by the lungs or other means. The

Roentgen studies show that, in the left lateral position, air can be delivered to the lungs, against the principle of air buoyancy, apparently by a combination of ventricular contraction and inspiratory aspiration. The apneic phase of the respiratory arrhythmia induced by venous air embolism tends to defeat the mechanisms of recovery by eliminating the inspiratory aspiration effect, and it is of utmost importance that the significance of this factor be recognized in the therapy of this condition. We have previously pointed out[12] that the minimal lethal dose of a gas injected into the circulation is considerably greater when respiration is artificially maintained than when the respiratory reflex disturbances are allowed free play. We have shown also that the minimal lethal dose is far less[7] in experiments involving an animal with a surgically opened thorax, even though intratracheal artificial respiration is maintained, and this is again due, undoubtedly, to the interference with the inspiratory aspirating effect of normal chest movements.

The possibility that some of the effects of venous air embolism may be due to bubbles which have passed through pulmonary capillaries, or arteriovenous anastomoses, to obstruct vital systemic arteries must be given consideration. We have searched for such bubbles and none has been found except in previous experiments in which repeated sublethal doses were given to animals on their left sides[8] and in animals with septal defects. None was found in the present study either by Roentgen evidence or at necropsy. The infrequent finding of such bubbles is in keeping with the studies of Chase in 1934[5], and those of the Curtillets[6]. The latter have shown that air disappears twice as fast from the lungs as it does from intestinal vessels or from the vessels in the frog's foot web. They found that high pressures (above 60 mm. Hg) are needed to force air through the pulmonary capillaries, and that, under ordinary circumstances, isolated air bubbles are stopped in arterioles of 30 to 40μ diameter. Inasmuch as Gordon *et al.*[9] have shown that arteriovenous vessels average 15 to 19μ in diameter, it seems unlikely that bubbles should be carried through, except when marked rises in pulmonary arterial pressure occur. It is possible that a sufficient rise in pressure occurs only when conditions are particularly unfavorable for recovery, as in the right-side-down position. It is true, of course, that if an interatrial or interventricular defect exists, air can be forced through such defects when the pressure rises sufficiently in the right heart to produce a venoarterial shunt. Cases of mixed venous and arterial air embolism due to such a shunt have been reported in the literature[10,15]. Generally speaking, however, it is probably very unusual for venous air embolism to be complicated by systemic arterial embolic involvement.

From our present understanding of the pathophysiology of venous air embolism, it would appear that the most adequate therapy to recommend for application in the human would be:

A. *Prophylaxis.* This would involve care to avoid all circumstances under which air embolism may occur, or the use of a highly soluble gas, such as carbon dioxide, for any injection which may result in embolism.

B. *Treatment of the embolic accident:*
   1. Immediate placement in the left lateral position.
   2. Artificial respiration.
   3. Aspiration of the right atrium if No. 1 and No. 2 are ineffective.

The opportunity has been afforded us recently to observe the films of a human case of venous air embolism complicating angiocardiography. The procedure was performed by means of a catheter in a cervical vein, since adequate peripheral veins were not available. The patient was in the sitting position. When the saline-containing syringe was disconnected to allow attachment of the one containing the Diodrast a sucking sound was heard. The patient collapsed, was unresponsive for a period of 2 minutes, had mild generalized convulsive movements, stertorous breathing and an intense bradycardia. Fortunately, complete recovery occurred very rapidly after the 2-minute period. It was thought by those doing the angiocardiographic examination that the reaction was due to Diodrast, but the films (Figs. 6A and 6B) showed that a bubble of gas (approximately 10 to 20 cc.) was trapped in the pulmonary artery and its left main branch. It will be noted from the films that the trapping occurred in the most superiorly located portion of the pulmonary artery in accordance with the principle of air-buoyancy, the patient being in the upright position. We believe this to be the first instance on record of the roentgenologic demonstration of pulmonary gas embolism in the human.

Summary. Biplane stereoscopic angiocardiography was used to study the basic pathophysiology of venous air embolism. It was found that air injected into the femoral vein in amounts approximating the average lethal dose appeared almost immediately within the Roentgen shadow of the heart and pulmonary artery. The presence of air in the latter structure correlated well with the presence of systemic hypotension and respiratory arrhythmia, but not with any significant blood chemical alteration. In the left-side-down position the amount of air in the pulmonary artery either fluctuated or progressively decreased in animals which recovered, and was generally reciprocally related to the amount of air in the right atrium and ventricle. In the latter chambers, the air was trapped away from the outflow tract of the right ventricle, so that continuity of blood column from the cavæ to the pulmonary artery was maintained. This evidently permitted circulation to continue until the air could be eliminated from the right heart by contraction or by inspiratory aspiration or both. By contrast, the supine position resulted in a very unfavorable situation, the blood column in the right heart being interrupted by an obstructing air trap located between the cavæ and the pulmonary artery. These studies thus confirm the importance of the left-side-down position in aiding recovery from venous air embolism.

A human case of venous air embolism associated with accidental aspiration of air during angiocardiography has been reported, together with roentgenograms demonstrating an air trap in the pulmonary artery.

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REFERENCES

1. **Aviado, D. M., Jr., Li, T. H., Kalow, W., Schmidt, C. F., Turnbull, G. L., Peskin, G. W., Hess, M. E.,** and **Weiss, A. J.**: Am. J. Physiol., **165**, 261, 1951.

2. **von Bezold, A.**, and **Hirt, L.**: Unters. Physiol. Lab., **1**, 73, 1867.
3. **Chamberlain, W. E.**, and **Stauffer, H. M.**: A Biplane Stereoscopic Angiocardiographic Device. Read before Symposium Neuroradiologicum, Serafimerlasarettet, Stockholm, Sept. 1952.
4. **Chamberlain, W. E.**, and **Stauffer, H. M.**: A New Device for Stereoscopic Cerebral and Cardiac Angiography. Read before Section on General Medicine, College of Physicians of Philadelphia, Oct. 22, 1951.
5. **Chase, W. H.**: Surg., Gynec., and Obstet., **59**, 569, 1934.
6. **Curtillet, E.**, and **Curtillet, A.**: Compt. rend. Soc. biol., **130**, 645, 647 and 650, 1939.
7. **Durant, T. M.**, **Long, J.**, and **Oppenheimer, M. J.**: Am. Heart J., **33**, 269, 1947.
8. **Durant, T. M.**, **Oppenheimer, M. J.**, **Webster, M. R.**, and **Long, J.**: Ibid, **38**, 1, 1949.
9. **Gordon, B. D.**, **Flasher, J.**, and **Drury, D. R.**: Am. J. Physiol., **173**, 275, 1953.
10. **Helper, T. K.**, **Truter, J. L.**, and **Hunt, H. F.**: Am. J. Clin. Path., **17**, 322, 1947.
11. **Martland, H. S.**: J. Am. Med. Assn., **129**, 905, 1945.
12. **Oppenheimer, M. J.**, **Durant, T. M.**, **Lynch, P. R.**, and **Weibber, D. L.**: Am. J. Med. Sci., **225**, 362, 1953.
13. **Rahn, H.**, **Stroud, R. C.**, and **Meier, H.**: J. Applied Physiol., **5**, 308, 1952.
14. **Russ, F. H.**, **Glenn, D. L.**, and **Gianturco, C.**: Radiology, **61**, 637, 1953.
15. **Thomassen, K.**: Norsk mag. f. laegevidensk., **99**, 470, 1938.

WEIGHT REDUCTION: A STUDY OF THE GROUP METHOD: REPORT OF PROGRESS

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In a preliminary paper in these pages we have previously reported on a study of the application of group methods to weight reduction[1]. Undertaken 3 years ago on a grant from the Bureau of Chronic Diseases in the California State Department of Public Health, the study aimed to determine the efficiency and effectiveness of a group method for helping large numbers of people to lose weight. More particular information is now available on the results of this experience with 325 overweight individuals who have been observed during their participation in 24 groups.

Procedure. These groups, formed from overweight people responding to public announcement or referred by physicians, usually contained about 12 members. They met weekly for 16 sessions, each lasting about an hour and a half. The 22 individuals who have had experience as leaders of these groups were chosen from professional fields which were presumed to include, as part of the discipline, either skill in working with people or knowledge of food. For example, psychology, social work, health education, public health nursing, nutrition and dietetics have provided leaders, in addition to medicine.

A 1000-calorie, balanced diet was prescribed, and the group members permitted, and encouraged, to discuss their problems (any problem, or those related especially to dieting, depending to a certain extent upon the background of the leader). Participation in the group was expected to be helpful by reinforcing the individual's determination to adhere to the diet.

During this period a great deal of information has been accumulated relevant to the personality, nutrition habits, and social behavior of overweight individuals. Much of this material has yet to be analyzed, but will be reported in detail as it becomes available. For example, a battery of psychological tests has been used for testing before, during, and after participation in group situations oriented toward weight loss. The information from these observations would seem to call for reevaluation of some current ideas about personality traits and social behavior of obese individuals.

An attempt was also made to get a history of each patient's overweight problem by using one or more of the following techniques: a brief history taken at the time of the physical examination, a self-administered health questionnaire, and a schedule of dietary habits and patterns which was completed by a nutritionist in an interview situation. This latter procedure was carried out at the beginning and at the end of group participation. The information elicited from each subject consisted of a family history of overweight, "heart trouble", and diabetes; the patient's history of overweight; the patient's attitude toward her weight problem and toward dieting; some simple social data; and information about meal patterns and eating habits. In addition, the results of participating in the group and follow-up records on weight changes have been tabulated. It is the analysis of some of the above material which is reported now.

Results. STUDY POPULATION. A total of 290 records have been analyzed for possibly significant items, 35 records having been excluded from the study for reasons which would tend to make weight information unreliable: for example, pregnancy, cast put on leg, hospitalization or illness with weight loss, failure to have weight recorded at the first or second meeting held for the

group to which assigned. Also excluded, because they unfortunately constitute such a relatively small group, were records on 9 men.

The 290 women who made up the study population were all volunteer participants who came specifically for weight reduction in response to a public notice. They ranged in age from 14 to 72, with a median age of 40.6 years. Of the total, 70% were married, 13% were single, and the remainder either widowed or divorced in approximately equal numbers. Of the 250 women on whom the information is available 76% had at least one child, with the average per woman slightly over two. The majority had children in an age range at which they would be still at home. Fifty-nine per cent of the total group was occupied with housewife duties and not working outside the home.

The participants ranged in height from 4 feet 7 inches to 5 feet 11 inches, with a median height of 5 feet 4 inches, and were predominately of medium frame. The range of weight at entry to the study was 116 to 347 pounds. With an initial median weight of 182.5 pounds, it can be seen that most participants had a serious weight problem.

HISTORY OF OVERWEIGHT. In questioning 188 participants about the beginnings of their overweight problems, it was noted that more than half this study population was able to associate initial weight gain with a single incident; 22% identified this incident as pregnancy. Illness or operation was named by the next largest group (13%). It is interesting that these incidents are associated with the reception of medical care and would thus seem to offer an opportunity for physicians to give timely help to patients at the start of a weight problem. Marriage, puberty, menopause, change of environment, and nonspecific emotional and social difficulties were other frequently named incidents (total: 26%) related to initial weight gain.

Most of the individuals have been overweight for a considerable period: 22.7 years was the median age at which first overweight was noticed. Since the median age of the study population is 40.6, this suggests that at least half the subjects had been overweight for almost 20 years, inasmuch as the great majority claimed that the weight burden had been maintained and usually increased after initial onset.

It would be unfair to assume that these people had passively maintained this unhealthy state, for 92% claimed they had tried to lose weight (for an average of two serious attempts), listing doctor's advice (including diet or medication, or both), self-initiated dieting, exercise, and reducing salons as among the methods tried. Only 6.4% stated they had ever reached a desirable weight in previous dieting attempts, while 6.8% stated they failed altogether to lose weight. The rest (87%) had an unsatisfactory experience with their attempts to reduce (that is, had "little" or "some" success but loss was not maintained).

DIETARY PATTERNS. An aspect of the overweight problem which, in these days of psychological ascendancy, gets but little attention is the question of eating habits and dietary patterns. Although admittedly a difficult area in which to get exact information, an attempt was made to tabulate answers to a few simple questions relating to this matter. For example, among 96 participants, 43% stated that during the day their periods of greatest hunger come between regularly scheduled meals. Only 8% checked the morning as the time they are hungriest. Poor breakfasts and eating between meals are habits of the overweight individual which are the frequent despair of doc-

tors and dietitians. The great majority eat regular meals, eat most of the meals at home and do their own cooking. It is interesting that 56% admitted to eating four or more times a day, including 18% who stated they "eat all day". Perhaps all this suggests that the usual professional attempts to get the overweight patient to eat a full breakfast and to avoid between-meal eating are out of step with a more compelling rhythm of hunger. One difficulty may lie in following the common practice of eating three regular meals a day and then feeling guilty about catering to an "off-beat" need for food. It is believed that a self-demand feeding schedule is best for youngsters. It might also be a more positive approach to overweight adult feeding problems.

In light of the current discussions on the importance of carbohydrate restriction by the overweight individual, it is interesting to note the great frequency with which, in the nutrition interview, bread was singled out as a favorite food or diet item which would be missed most while reducing. This is reflected in the 48% of 188 participants who stated that they eat more than 4 slices of bread a day, including 13% who eat more than 7 slices a day.

FAMILY PATTERNS OF OBESITY. The tendency for families to follow a pattern of obesity is frequently seen. Apparently the risk of obesity is greater in families with other obese members. Among 290 subjects, 231 had a total of 803 overweight immediate family members, a ratio per participant of 3.5. Of the 231, 40% had 4 or more obese family members, including 22 subjects who had 7 or more obese members in the immediate family. This information was elicited for grandparents, parents, siblings, and children. Female relatives predominate, with a ratio to males of 1.6. This ratio is somewhat less pronounced, however, between brother and sister; perhaps this points to the mother who prepares the meals and, to a large extent, sets the family eating pattern.

Is it possible that among these overweight families we find more heart disease and diabetes? The occurrence of "heart trouble" among immediate family members of our overweight subjects (a ratio of 1.7 per participant) and of diabetes (a ratio of 1.3 per participant) perhaps is high.

RESULTS OF GROUP PARTICIPITION. Among the many ways of testing the degree of success of a particular method used in weight reduction are: 1) simple measurement of the pounds lost (which has obvious limitations); 2) calculation of the percent of total weight lost or percent of overweight lost (both inadequate and unfair, in that it places a disproportionate burden on those most overweight, even though they excel in total weight lost); 3) comparison of observed weight loss with expected weight loss (ref. the Performance Index of Jolliffe and Alpert)[2]. The last is reliable and should be adopted for the evaluation of weight reduction programs; if done throughout the country, comparability of research results would be possible. We, not being familiar with the Performance Index at the beginning of our study, arbitrarily assigned a 2-pound loss per week per person goal. This proved a poor measure to use, because of the difficulty of estimating adherence to the diet. In addition, intermittent attendance at the group meetings, and drop-outs, made difficult the choice of some standard for achievement.

Since measurement of the effect of group participation was our primary objective, we were interested in the high correlation shown between weight loss and meeting attendance: 259 (89%) of all participants, lost weight

and of these, 207 (80%) attended half or more of the sessions held for the group to which assigned. In terms of amounts of weight lost, 152 people lost more than 10 pounds (10 to 52 pounds), of whom 111 attended at least three-quarters of the meetings held, while of the 66 participants who lost more than 20 pounds (20 to 52 pounds) 57 attended at least this number of meetings. Refer to Table 1.

To this point our concern has been primarily with the first aspect, that is, the testing of the efficiency of the group method for effecting weight loss. Entirely different or at least additional mechanisms, we believe, are involved in the latter, the maintenance of weight loss, which we have only begun to investigate.

Follow-up for weight changes is currently under way. The small numbers

TABLE 1.—NUMBER OF PARTICIPANTS BY POUNDS WEIGHT CHANGE AND PERCENT OF MEETINGS ATTENDED*

Pounds Weight Change During Meetings Attended	*Number of Participants by Percent of Meetings Attended*			
	Total	*50*	*50 to 75*	*75 or More*
Total	290	71	73	146
Loss	259	52	66	141
10	107	47	30	30
10-19	86	5	27	54
20-29	49		5	44
30 or more†	17		4	13
No loss	31	19	7	5
Stayed Same	13	9	3	1
Gained‡	18	10	4	4

*Twenty-four groups held an average of 16 meetings each.

†Range: 30-52 pounds.

‡Average gain was 3 pounds.

It is too easy to attribute to participation in the groups the success of those who did lose weight. It is likely that the degree of motivation determined the extent of an individual's participation as well as weight loss. On the other hand, as cited earlier, most of the people had tried many times, unsuccessfully, to lose weight and we believe that participation in the groups will be found to be significant when an opportunity is presented to test this factor carefully.

FOLLOW-UP INFORMATION. A weight reduction program to be considered successful must 1) result in the reduction of the majority of individuals to ideal weight within the time period necessary for this to be achieved, and 2) result in the maintenance of ideal weight by the majority.

and relatively brief period make this information inconclusive. The trend, however, seems to be in the direction of disappointing results, both from the standpoint of continued loss and also maintenance of weight loss achieved in the group situation. Follow-up records were obtained more easily from those whose attendance was good during the observation period. It was virtually impossible to obtain a record from those who had attended less than a quarter of their meetings.

Discussion and Conclusions. 1) Case histories of overweight people (including familial occurrence, incidents at onset, length of time overweight, the discouraging history of dieting in the face of hunger or appetite) all would suggest the urgent need for preventive programs. The physician in office or

clinic practice has a frequent opportunity to observe the beginning of weight gain and to help the patient prevent the accumulation of a weight problem detrimental to his health in the years to come.

2) Weight reduction for most people is not a simple matter of seeing the physician and receiving from him a sensible diet to follow. Weight loss is surely produced by decreased caloric intake but adherence to a lessened intake over a long enough period of time to achieve permanent reduction is the *sine qua non* of weight correction. Such adherence by the overweight patient is not the usual experience of many physicians.

3) The crucial role of motives for dieting is recognized and calls for study. No method directed toward the control of obesity has been 100% successful. The "will" of the individual appears to be very important for the success of any such plan. We are becoming increasingly aware of the importance of factors which influence the strength and direction of the "will" of the individual, for example, hereditary, educational, nutritional, social and cultural factors in addition to the frequently considered sole factor of orexia nervosa.

It is interesting to speculate on how much the importance of "will" would diminish, even if we had a specific remedy for overweight. There are specific remedies for other conditions which, yet, retain their standing as problems in public health. One woman in our group spoke feelingly for many when she said, "We don't like it this way, but it's hard to do anything about it when fat doesn't hurt."

4) Adaptations of methods for working with overweight people in groups will be found valuable. In addition to the saving of staff time, such techniques provide an efficient means for providing accurate information in answer to specific concerns about overweight and dieting. It also offers a sympathetic setting in which patients can be urged to talk and given the time to do so. Our observations thus far suggest that the recognition and acceptance by a group, the wholesome effect of group discussion, the persuasiveness of group decisions, the reassurance, support and competition which each individual feels from his identification with a group of people having the same problem and doing something about it, are all potent factors for success.

It has been noted that the groups, in general, have centered their interest in the same discussion topics. The influence of the leader's professional background probably accounts for differences in emphasis or timing, but the same subjects recur in each group. Several professions seem able to contribute to useful group discussions, but our observations, although inconclusive, indicate the relatively greater importance of skill in handling people.

5) Discussion with participants, both those who lost significant amounts of weight and those who didn't, as well as evidence from their histories of dieting, tends to support the impression that the group experience helped more than anything which had been offered in their previous attempts to lose weight. This is revealed in the results which indicate that satisfactory weight loss can be expected from the majority of participants in groups. On the other hand, we are faced with the necessity for improving the group approach to insure permanent weight loss. A longer period of support in the group environment (an almost universal request) may be one missing factor.

REFERENCES

1. **Harvey, H. I.,** and **Simmons, W. D.:** Am. J. Med. Sci., **225,** 623, 1953.
2. **Jolliffe, N.,** and **Alpert, E.:** Postgrad. Med., **9,** 106, 1951.

THE CHOICE OF AN ANTICOAGULANT

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The anticoagulant of choice should afford the patient the greatest possible protection against thromboembolic complications but, at the same time, it should not be toxic. The convenience of administration, ease of controlling therapy and suitable laboratory requirements are also to be considered but are of secondary importance.

At the Toronto General Hospital a clinical study of 4 of the currently acceptable anticoagulants was undertaken with the aim of comparing their relative effectiveness and hazards.

Method. Patients on the public ward Services of Medicine, Surgery, Obstetrics and Gynecology who were suspected of having thromboembolic disorders were seen in consultation by the authors. As soon as a provisional diagnosis of thromboembolism had been made, one of the anticoagulants was assigned by random distribution to the patient. The anticoagulants used were heparin, Dicumarol, phenylindanedione and cyclocumarol. Heparin was given by intramuscular injection at 12-hour intervals in doses sufficient to produce a maximum prolongation of clotting time of 2 to 3 times the normal value. The usual dose required was 15,000 units twice daily. The other 3 anticoagulants were given orally and their effect was measured by daily prothrombin determinations (Quick's one-stage method).

A dilution curve of normal plasma was prepared for each solution of thromboplastin (Difco). Prothrombin levels between 10 and 30% of normal were considered within a satisfactory therapeutic range. When one of the anticoagulants had been assigned to a patient, the therapy was initiated and maintained by the resident staff subject to advice from the authors who recorded the clinical progress.

In the first phase of this investigation 489 patients received anticoagulant treatment. (See Table 1.) Cases were classed as "suspected" when definite confirmatory evidence for the diagnosis was not obtained from the subsequent clinical course, the laboratory findings or the electrocardiograph. The suspected cases were not included in the comparison of the effectiveness of the different anticoagulants, but were included in the consideration of toxic effects. Patients dying during the first 48 hours of treatment were excluded from all consideration since oral anticoagulants are often not effective within this time. The "miscellaneous" group consisted of a variety of conditions including thromboangiitis obliterans, congestive failure and peripheral emboli.

Results. A COMPARISON OF EFFECTIVENESS. Too few deaths occurred to allow a statistical comparison of the mortality rates. Thromboembolic complications occurring in the "definite" cases after commencement of treatment were more numerous and were subjected to statistical analysis. The apparent differences between the various treatments were not significant. (See Table 2.) A control group could not be included because of the undesirability of withholding a treatment that current opinion favored. Accordingly, from these comparative results, one might say that all the drugs were equally effective or equally ineffective.

B. INCIDENCE OF HEMORRHAGE. In this study, 5.7% of the patients suffered bleeding that was severe enough to necessitate termination of treatment. The hemorrhagic complications are summarized in Table 3; they have been reported in detail elsewhere[2].

Treatment with any drug that interferes with blood coagulation carries with it a risk of bleeding. With the oral drugs used in this study, it appeared that the more consistently the therapeutic level was maintained the more frequently spontaneous bleeding occurred. This is in keeping with the view that hemorrhage from these drugs is related to the degree of prothrombin depression rather than to other intrinsic properties.

A very small dose of cyclocumarol would maintain a low prothrombin level and this depression persisted longer when the drug was discontinued than in the case of Dicumarol or phenylindanedione. Any of these drugs caused occasional depression of the prothrombin level below 10%. When this happened in patients receiving cyclocumarol, the return to normal was unduly delayed because of its prolonged action. This was reflected by a higher percentage of prothrombin levels below 10% (Table 4) and by a greater incidence of bleeding (Table 3). Although vitamin K_1 emulsion (50 mg. intravenously) was rapidly effective in restoring safe prothrombin levels in patients receiving any of the oral anticoagulants, there was always the danger that serious hemorrhage might occur before vitamin K_1 became effective.

The intramuscular administration of heparin was associated with a signifi-

TABLE 1.—THROMBOEMBOLIC COMPLICATIONS AND MORTALITY IN 489 PATIENTS TREATED WITH ANTICOAGULANTS

			Thromboembolic Complications		*Deaths*	
Diagnosis		*No.*	*No.*	*%*	*No.*	*%*
Myocardial Infarction:	Suspected	66				
	Definite	210	27	13	*20	9.6
Pulmonary Infarction:	Suspected	18				
	Definite	59	5	8	0	
Venous Thrombosis:	Suspected	16				
	Definite	96	9	8.3	**4	4.1
Miscellaneous:		24	1	4.1	0	
Total		489	42	8.6	24	4.9

* Includes 3 deaths associated with hemorrhage.
** Includes one death associated with hemorrhage.

TABLE 2.—COMPARISON OF EFFECTIVENESS OF FOUR ANTICOAGULANTS IN 365 PATIENTS WITH DEFINITE THROMBOEMBOLIC DISORDERS

		Further Thromboembolic Episode	
Treatment	*Number of Cases*	*Number*	*%*
Heparin	84	13	15
Dicumarol	93	7	7.5
Phenylindanedione	97	8	8.1
Cyclocumarol	91	13	14
Total	365	41	11.2

TABLE 3.—INCIDENCE OF HEMORRHAGE

Treatment	*Number of Cases*	*Hemorrhagic Complications %*
Heparin (I. M.)	112	15.0
Dicumarol	123	3.4
Phenylindanedione	133	0
Cyclocumarol	121	5.8
Total	489	5.7

cantly higher incidence of bleeding (Table 3). This was true even when bleeding at the sites of injection was excluded. In addition, this administration of heparin caused considerable local pain in a number of patients.

After the review of these 489 patients had been completed it was decided to use only Dicumarol and phenylindanedione for prolonged anticoagulant therapy. No toxic effects of any kind were observed in the first 143 patients who received phenylindanedione[1]. With continued use of this drug, agranulocytosis developed in 2 patients.

TABLE 4.—MAINTENANCE OF THERAPY WITH ORAL ANTICOAGULANTS*

Drug	Daily Prothrombin Times: Percentage in Therapeutic Range	Daily Prothrombin Times: Percentage below 10%	Average Daily Dose Mg.
Cyclocumarol	68.7	7.2	17.9
Dicumarol	63.0	1.6	53.4
Phenylindanedione	50.0	0.1	92.5

* Based on 20 patients on each drug.

Case Reports. CASE 1. Mrs. G. S., aged 57, received phenylindanedione daily for 28 days following a myocardial infarct. The amount of drug required was not unusual and the depression of prothrombin level was satisfactory. Three days before the drug was discontinued the patient's temperature rose to 102° F. and râles were heard over the base of the left lung. A diagnosis of bronchopneumonia was made. Penicillin and streptomycin were begun and in the next 2 days the fever became less. The leukocyte count, which had been 11,800 on admission, was found to be 3,000; phenylindanedione was discontinued. During the next week the patient remained well except for slight fever, the temperature reaching 100° F. on several occasions. The leukocyte count continued to range around 3,000. Twelve days after stopping phenylindanedione the temperature rose to 103.8° and the leukocyte count fell to 1,200. On the following day she had a severe chill with a temperature of 105°. The leukocyte count had fallen to 900 and only lymphocytes were seen in the stained blood film. Red cells and platelets appeared normal. A marked reduction in the granulocyte series was noted in the sternal bone marrow. A culture of *Bacillus pyocyaneus* was obtained from the blood. ACTH was given intravenously, and aureomycin by mouth. During the next 2 days there was no change in either the clinical condition or the leukocyte count. On the third day the temperature fell with a return of young granulocytes in the peripheral smear. The leukocyte count then rose to 6,000 where it remained until the patient's discharge from the hospital 2 weeks later.

CASE 2. Mrs. H. M., aged 64, received treatment for phlebitis following a Judet arthroplasty of the left hip. The signs of phlebitis slowly decreased and, after 21 days of treatment, phenylindanedione was discontinued. One week later an exacerbation of phlebitis occurred and the drug was given again. After 4 days the patient became drowsy and complained of severe headache. The temperature was 101.4° F., and several papules appeared over the buttocks which were itchy at first and later became painful. The leukocyte count was found to be 600 cells, and phenylindanedione was discontinued. A few eosinophils were the only granulocytes seen in the smear. Before operation the count had been 6,900, and the platelets and red cells normal. ACTH, cortisone, blood transfusions, penicillin and streptomycin were given without avail; the patient died 6 days later. The lesions of the buttock had become necrotic, followed by widespread necrosis of skin and subcutaneous tissues of the back. In addition to phenylindanedione this patient had received aureomycin, 500 mg. daily for 5 days, followed by terramycin, 500 mg. daily for a week. This latter drug was stopped one week before the onset of agranulocytosis.

These 2 cases of agranulocytosis occurred among 261 patients treated with phenylindanedione. When the second patient (Mrs. H. M.) died, it was decided to discontinue phenylindanedione therapy although one could not say with certainty that this drug was responsible for the agranulocytosis. The probability seemed greater when Cameron[3] reported a case of agranulocytosis in his series. The actual incidence will be determined by total medical experience.

Discussion. From our study we did not find any difference between the anticoagulants in their ability to prevent further thromboembolic complications. There was a difference, however, in toxic manifestations. Heparin administered intramuscularly caused more bleeding than Dicumarol and phenylindanedione. Accordingly, it seems reasonable that the heparin therapy should be reserved for patients requiring rapid initiation of anticoagulant effect. It should then be discontinued when the oral anticoagulant has reduced the prothrombin level sufficiently. Of the oral anticoagulants studied, cyclocumarol caused more bleeding than the other two, probably because of the prolonged action of this drug. Phenylindanedione at first appeared to be a very useful drug with certain minor advantages over Dicumarol[1]. However, the occurrence of 2 cases of agranulocytosis in 261 patients receiving phenylindanedione makes one hesitant about further use of this drug. In the future it may be shown that the risk is not as great as it would appear to be from our series but it is one that must be considered. From our experience, Dicumarol appears to be the most satisfactory preparation for maintained anticoagulant treatment of thromboembolic disorders.

Summary. 1. Four different anticoagulants were assigned at random to patients with thromboembolic disorders. The preparations included heparin (10,000 units per cc.) for intramuscular administration, Dicumarol, phenylindanedione and cyclocumarol. In the first part of the study 489 patients were treated and of these 365 were considered to have definite thromboembolic disorders.

2. All 4 anticoagulants were equally effective (or ineffective) in the prevention of further thromboembolic complications.

3. In 5.7% of patients, significant bleeding occurred. The incidence of hemorrhage was greater when heparin and cyclocumarol were used. Heparin should be reserved for the rapid initiation of anticoagulant therapy.

4. Agranulocytosis developed in 2 patients out of the 261 who received phenylindanedione.

5. Dicumarol appears to be the anticoagulant of choice on the basis of this study.

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REFERENCES

1. **Brown, K. W. G.**, and **MacMillan, R. L.**: Am. J. Med. Sci., **225**, 495, 1953.
2. **MacMillan, R. L.**, and **Brown, K. W. G.**: Canad. Med. Assn. J., **69**, 279, 1953.
3. **Townsend, S. R., Fay, K. J., Downing, J. R., Laing, R.**, and **Cameron, D. C.**: Canad. Med. Assn. J., **69**, 149, 1953.

QUINIDINE IN THE TREATMENT OF AURICULAR FIBRILLATION

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The value of quinine in the treatment of auricular fibrillation was first indicated by Wenckebach in 1914. Although quinidine was isolated by Frey in 1918, extensive studies of its action have been limited to the literature of the past 10 years.

Initial reports on quinidine overemphasized the danger of this drug so that considerable fear still exists among practitioners and even cardiologists as to its toxicity. However, the danger of auricular fibrillation which is a frequent cause of heart failure and always a potential source of embolism, overshadows the danger of quinidine. "In patients with organic heart disease, the occurrence of auricular fibrillation, even with a comparatively slow ventricular rate, may so lower the cardiac output that heart failure occurs or persists in spite of treatment"[3]. On the other hand reversion to normal sinus rhythm increases cardiac output and diminishes the frequency of embolism[5].

Since the clinical use of quinidine is still under discussion, it was thought worth while to report our own experience in the treatment of auricular fibrillation with quinidine. This report deals with short term results, that is, results obtained on hospitalized patients during their stay in the hospital. The long term results, namely results obtained on the same patients outside the hospital will be the subject of a later communication.

Method. This report is based on observation of 67 cases of auricular fibrillation treated at the Ottawa General Hospital from 1948 to 1952. All these cases were admitted to the hospital because of congestive heart failure and received adequate treatment for this condition prior to quinidine therapy. Auricular fibrillation was present in all cases but in many its exact duration could not be ascertained. The patients were unselected and all were treated according to the same schedule.

The cases may be divided into 3 groups according to the etiology of the underlying cardiac disease (Table 1).

TABLE 1.—ETIOLOGY OF AURICULAR FIBRILLATION IN THE PRESENT SERIES

Group	*No. of cases*	*%*
1. Arteriosclerotic heart disease	39	58
2. Hypertensive heart disease	7	11
3. Rheumatic heart disease	21	31
Total	67	100

The age of the 67 patients varied from 26 to 84 years. The age range and mean age in each etiologic group is shown in Table 2.

TABLE 2.—DISTRIBUTION OF PATIENTS ACCORDING TO AGE

Group	*Range in years*	*Mean in years*
1. Arteriosclerotic heart disease	45 to 84	67
2. Hypertensive heart disease	43 to 77	61.5
3. Rheumatic heart disease	26 to 58	41.6

Treatment was carried out according to the following schedule:

First day	quinidine	0.2 gm. times 1
Second day	"	0.2 gm. times 3
Third day	"	0.2 gm. times 6
Fourth day	"	0.3 gm. times 6
Fifth day	"	0.4 gm. times 6
Sixth day	"	0.5 gm. times 6
Seventh day	"	0.6 gm. times 6
Eighth day	"	0.7 gm. times 6
Ninth day	"	0.8 gm. times 6
Tenth day	"	0.9 gm. times 6
Eleventh day	"	1.0 gm. times 6

The first day's dose was given to test the patient's sensitivity to quinidine. If there were side-reactions quinidine therapy was not given. Two patients are not included in this study because one experienced generalized erythema and the other developed pallor, palpitations and a fall in blood pressure after the test dose. When the heart rhythm became clinically regular at any of the above mentioned doses an electrocardiogram was taken to verify the clinical impression. When the dose of 0.6 gm. times 6, that is, 3.6 gm., was reached an electrocardiogram was taken in order to ascertain whether there were any signs of toxicity. Any further increase of the dosage was dependent on whether a conduction defect developed. When reversion to normal sinus rhythm occurred, the dose necessary for this reversion was maintained for 24 hours. If this dose was 0.5 gm. times 6, or greater, the dose was progressively decreased by 0.1 gm. times 6 daily until an arbitrary maintenance dose of 0.2 gm. times 6 was reached. If the dose necessary for reversion to sinus rhythm was less than 0.5 gm. times 6, then the daily dose was progressively decreased by 0.1 gm. times 6 until an arbitrary maintenance dose of 0.2 gm. times 3 was reached. If the heart rate rose above 90 beats per minute, or if a few premature beats appeared, the maintenance dose was stabilized at that level. If auricular fibrillation recurred either because of a too rapid decrease of the dosage or because the patient omitted to take quinidine, the dose which had been necessary for reversion was given, and the maintenance dose fixed 0.1 gm. times 6 higher than the dose on which relapse occurred. A maintenance dose of digitalis leaf (0.1 gm.) daily was administered during the treatment with quinidine except when the pulse rate was slow (about 60), or when an increase of the P-R interval appeared in the electrocardiogram. In such an event, digitalis was stopped but quinidine was continued. No anticoagulant therapy was used prior to quinidine and the concentration of quinidine in the plasma was not determined.

Results. In Table 3 the incidence of reversion of auricular fibrillation to normal sinus rhythm with quinidine is summarized.

In Table 4 these data are tabulated according to the etiological types of heart disease with which auricular fibrillation was associated.

TABLE 3.—INCIDENCE OF REVERSION OF AURICULAR FIBRILLATION TO SINUS RHYTHM

Results	*Number of cases*	*%*
Reversion	60	89
Failure	7	11

TABLE 4.—INCIDENCE OF REVERSION OF AURICULAR FIBRILLATION TO SINUS RHYTHM IN VARIOUS ETIOLOGIC TYPES OF HEART DISEASE

Group	*Total group of cases*	*No. of cases*	*%*
1. Arteriosclerotic heart disease	39	35	90
2. Hypertensive heart disease	7	7	100
3. Rheumatic heart disease	21	18	86

This table would indicate that the highest reversion rates are to be obtained in auricular fibrillation associated with hypertensive heart disease and the lowest in auricular fibrillation due to rheumatic heart disease. However, the relatively small number of cases does not permit a well-founded conclusion in this respect and it is likely that the chances of reversion to sinus rhythm are approximately equal in the above 3 groups.

The range of total daily dose of quinidine and the mean dose at which reversion to normal sinus rhythm occurred in the various etiologic groups is presented in Table 5.

TABLE 5.—DOSE OF QUINIDINE NECESSARY FOR REVERSION

Group	*Range gm.*	*Mean dose gm.*
1. Arteriosclerotic heart disease	1.2 to 5.4	2.50
2. Hypertensive heart disease	1.2 to 4.2	1.98
3. Rheumatic heart disease	1.8 to 4.2	2.76

It would appear that the smallest dose needed for reversion is to be

found in hypertensive heart disease and the largest in rheumatic heart disease, but once again the small number of cases does not justify such a conclusion.

The daily doses of quinidine used for maintenance are presented in Table 6.

It would appear from this table that it is more difficult to maintain normal sinus rhythm after reversion in rheumatic heart disease than in arteriosclerotic or hypertensive heart disease. This is also suggested by the number of cases that relapsed during their stay in the hospital and which are distributed as follows (Table 7):

Complications or side effects of treatment occurred in 42% of the 67 patients. In 11% (7 patients) it was deemed advisable to stop the therapy before reversion to normal sinus rhythm was accomplished (Table 8).

In Table 9 the nature of the side effects and complications that appeared during the course of the treatment are tabulated. In some cases many symptoms were present simultaneously.

Most of the complications were so mild that they did not interfere with the treatment and disappeared when the dose was decreased. These included nausea, vomiting or diarrhea.

TABLE 6.—MAINTENANCE DOSE OF QUINIDINE

Group	*Range gm.*	*Mean dose gm.*
1. Arteriosclerotic heart disease	0.4 to 1.8	0.22, 4 times per day
2. Hypertensive heart disease	0.6 to 1.2	0.22, 4 times per day
3. Rheumatic heart disease	0.2 to 2.4	0.20, 6 times per day

TABLE 7.—CASES WHICH RELAPSED AFTER REVERSION

Group	*Total No. of cases that reverted to normal sinus rhythm*	*Number of relapse*	*%*
1. Arteriosclerotic heart disease	35	1	3
3. Rheumatic heart disease	18	4	22

The relapses were due in part to lack of cooperation on the part of the patient, and in part to a too rapid decrease in the dose. All of these cases reverted to normal sinus rhythm when the dose necessary for reversion was given again, but 2 cases relapsed 4 times, each time requiring the same dose for reconversion.

TABLE 8.—COMPLICATIONS AND SIDE EFFECTS

Reversion to Sinus Rhythm	*No. of Cases*	*%*
Without Complication	39	58
With Complication or Side Effects	21	31
Failure to revert due to complications or Side Effects	7	11

TABLE 9.—SIDE EFFECTS AND COMPLICATIONS

Symptoms	*No. of cases*
1. Gastrointestinal symptoms	15
2. Nervous symptoms	7
3. Electrocardiographic changes	6
4. Drop in blood pressure	1
5. Embolism	3

In 6 cases the complications or side effects were of such a nature that the treatment was stopped. Multiple embolism, severe cinchonism and severe gastrointestinal symptoms were present in each of 3 patients. Multiple electrocardiographic abnormalities which in-

cluded various degrees of heart block appeared in 2 patients. A generalized scarlatiniform rash on the third day of the treatment schedule occurred in the sixth case. A seventh patient with complete heart block prior to quinidine therapy did not revert to sinus rhythm on a dose of 1.8 gm. (0.3 gm. times 6) so the drug was discontinued.

Seven patients died during or after quinidine therapy. The causes of death are shown in Table 10.

TABLE 10.—CAUSES OF DEATH DURING TREATMENT

Causes of Death	*No. of cases*
Sudden death (cause undetermined)	3
Embolic	2
Bronchopneumonia	1
Senile psychosis	1

A brief summary of the course of events in each of the fatal cases is presented below:

Case Reports. CASE 1: Miss L. P., 72 years of age. Diagnosis: Arteriosclerotic heart disease with congestive heart failure, auricular fibrillation and right bundle branch block. Reversion to normal sinus rhythm occurred on the sixth day of the quinidine treatment schedule (0.5 gm. times 6). Death occurred suddenly that day with no signs of paralysis. No necropsy was performed.

CASE 2: Mr. C. B., 44 years of age. Diagnosis: Inactive rheumatic heart disease with mitral stenosis, congestive failure of many years duration and auricular fibrillation. Reversion to normal sinus rhythm on the seventh day of quinidine therapy (0.6 gm. times 6), with subsequent maintenance dose of 0.2 gm. times 6 for 5 days. Sudden death occurred on this day. No necropsy was performed.

CASE 3: Mr. A. R., 52 years of age. Diagnosis: Arteriosclerotic heart disease with congestive heart failure. Previous history suggested pulmonary embolism. Reversion to normal sinus rhythm on the seventh day of the treatment schedule (0.6 gm. times 6) with subsequent reduction to a maintenance dose of 0.2 gm. times 3 for 6 days. Death occurred suddenly. No necropsy was performed.

CASE 4: Mr. C.-E. R., 42 years of age. Diagnosis: Inactive rheumatic heart disease, mitral stenosis and auricular fibrillation. On the third day of the quinidine treatment schedule (0.2 gms. times 6), while auricular fibrillation persisted, the patient became unconscious with signs of left-sided hemiplegia. The drug was stopped at once. Two subsequent embolic episodes occurred during the 3 weeks which resulted in death.

CASE 5: Mr. A. H., 79 years of age. Diagnosis: Arteriosclerotic heart disease with congestive heart failure and auricular fibrillation. Reversion to sinus rhythm on the seventh day of quinidine therapy (0.6 gm. times 6), with subsequent reduction to a maintenance dose of 0.2 gm. times 6. After one week this dose was discontinued because of nausea, vomiting and anorexia. Auricular fibrillation recurred 6 days later and on the seventh day the patient developed right-sided hemiplegia with coma and died a few hours later.

CASE 6: Mr. O. L., 64 years of age. Diagnosis: Arteriosclerotic heart disease with congestive heart failure and auricular fibrillation; pulmonary emphysema. Reversion to normal rhythm on the fifth day of quinidine (0.4 gm. times 6) with subsequent reduction to a maintenance dose of 0.2 gm. times 4. The patient developed bronchopneumonia while in hospital and died. The cause of death was verified at necropsy.

CASE 7: Mr. A. V., 70 years of age. Diagnosis: Generalized arteriosclerosis, senile psychosis, arteriosclerotic heart disease with auricular fibrillation. Reversion to sinus rhythm on the fifth day of quinidine (0.4 gm. times 6) with subsequent reduction to a maintenance dose of 0.2 gm. times 3. The patient remained confused, disoriented and would not eat. He became progressively weaker and died 3 weeks later.

The first 3 case summaries indicate that quinidine therapy may have had a causative relationship to death. The sequence of events or the causes of death in the other 4 cases would seem to exonerate the therapy. If this conclusion is accepted the incidence of death possibly due to therapy would be 4.5%. This figure agrees with the mortality ascribed to quinidine therapy by other authors[1-9].

Comment. Evidence has been presented that auricular fibrillation can be converted to normal sinus rhythm

in the great majority of patients with hypertensive, arteriosclerotic or chronic rheumatic heart disease by quinidine therapy. In fact, failure to accomplish reversion to normal sinus rhythm was experienced about once in every 10 attempts (11%). These failures were due to the complications or side effects and their number might be reduced by the exclusion from treatment of patients with evidence of serious conduction defects. Age is not a contraindication to quinidine therapy. Ninety per cent of the patients with arteriosclerotic heart disease (the advanced age group) reverted to normal rhythm at a mean dose of quinidine which was less than the mean dose required for reversion in patients with rheumatic heart disease (the youngest age group). The results indicate that previous heart failure should not exclude the use of quinidine.

If it is accepted that auricular fibrillation is an uneconomical type of heart rhythm, we may conclude from this study that correction of the arrhythmia by quinidine therapy in patients with treated heart failure is practical. The mortality rate of 4.5% possibly due to the drug is not considered excessive in view of the serious nature of the underlying heart disease. These results confirm the following opinion of Askey[1]: "The references from data studied agree with the opinion that quinidine is a drug feared much more than it deserves to be and probably it is not used in many instances where it should be."

Summary. 1. Short-term results of the effect of quinidine on auricular fibrillation in 67 patients with heart failure, previously treated by conventional measures, have been presented.

2. Reversion to normal sinus rhythm was accomplished in 89% of the cases.

3. The presence of serious conduction defects is considered a contraindication to quinidine therapy.

4. Death may have been precipitated by quinidine in 4.5% of these patients.

REFERENCES

1. **Askey, J. M.**: Ann. Int. Med., **24**, 371, 1946.
2. **Carter, J. B.**: Med. Clin. N. America, **29**, 215, 1945.
3. **Goldberger, E.**: Heart Disease: Its Diagnosis and Treatment. Philadelphia, Lea & Febiger, 1951.
4. **Goldman, M. J.**: Am. Heart J., **40**, 93, 1950.
5. **Griggs, D. E., Stevens, H. G.**, and **Hadley, G. G.**: Med. Clin. N. America, **36**, 1025, 1952.
6. **Kory, R. C.**, and **Meneely, G. R.**: J. Clin. Invest., **30**, 653, 1951.
7. **Lewis, W. H., Jr.**: Ann. West. Med. & Surg., **5**, 1004, 1951.
8. **Weisman, S. A.**: California & West. Med., **63**, 125, 1945.
9. **Yount, E. H., Rosenblum, M.**, and **McMillan, R. L.**: Arch Int. Med., **89**, 63, 1952.

THE EFFECT OF CHRONIC AURICULAR FIBRILLATION ON THE OPERATIVE RISK

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This paper reports our observations on the operative risk of patients with organic heart disease and chronic auricular fibrillation. The preoperative status is correlated with the operative and postoperative course of 60 patients with chronic auricular fibrillation who had been subjected to 76 operations at Memorial Center during the period January 1, 1946, to February 29, 1952. During this same period, 34,344 operations were performed at this hospital.

Method. The hospital charts were reviewed for all patients with auricular fibrillation who were submitted to at least one major operative procedure of one hour's duration or more, under general and/or spinal anesthesia. The data were tabulated with regard to age, sex, race, cardiac history and status (according to the criteria of the New York Heart Association), complicating medical diseases, and the primary neoplastic process. The preanesthetic medications, the anesthesia, operative course, fluid and blood replacement, and complications incurred were reviewed with attention to the blood pressure, pulse, and respiratory variations. The postoperative status of the patient was studied with particular regard to the fluid and electrolyte balance, and the incidence of cardiorespiratory, genitourinary, neuromuscular, and other complications as related to the cardiac status, including the influence of cardiotonic and other medications. The course of the patients after discharge was reviewed according to the cardiac status, as well as the end results in the treatment of the neoplastic process. The extent of the cardiovascular complications occurring during operation was classified as *mild*, if the change in pulse and blood pressure varied from 10 to 14% of the preinduction level and did not exceed 15 minutes' duration; *moderate*, if the changes lasted up to 30 minutes or represented 15 to 25% variation; or *severe*, if the changes exceeded the previous limits in degree or duration.

Complications in the postoperative period were classified as cardiorespiratory, if, in that period, there developed pneumonia, pneumonitis, pulmonary atelectasis, pulmonary embolism, congestive heart failure, cerebrovascular accident, myocardial infarction, pericarditis, or increased myocardial disease and/or ischemia as indicated in the postoperative electrocardiogram.

Results. The primary pathological diagnoses of these patients are listed in Table 1. Nine (17%) of the 53 patients with malignant lesions had multiple primary cancers. Of the 60 patients undergoing 76 operations, there were 34 instances of mild, 16 of moderate, and 4 of severe cardiovascular complications during operation. There were 17 postoperative cardiopulmonary complications, including 3 postoperative deaths. Fifteen (25%) of the 60 patients have died of cardiovascular disease within 39 months: one postoperatively, 5 within 6 months of operation, and the remaining 9, from 12 to 39 months postoperatively.

No significant correlation was found between the incidence of operative cardiovascular complications and the development of postoperative cardiopulmonary complications.

PREOPERATIVE STATUS AND CORRELATION WITH COMPLICATION AND MORTALITY RATE. No significant correlation between age, sex, race, and postoperative complications or cardiovascular deaths could be made. Thirty-seven patients were male and 23 female; 58 were white and 2 Negro. The youngest patient was 29, the oldest 87, with a mean of 64.4 years and a median of 65 years; 71% were 60 years of age or older.

TABLE 1.—PRIMARY PATHOLOGICAL DIAGNOSES BY REGIONAL DISTRIBUTION

	Number of Patients	
Head and Neck Lesions		21
Cancer of Skin	3	
Malignant Melanoma	1	
Cancer of Lip, Tongue, and Mouth	14	
Cancer of Extrinsic Larynx	1	
Cancer of Thyroid Gland	1	
Nontoxic Substernal Thyroid Adenoma	1	
Breast Lesions		10
Cancer	8	
Benign Tumors	2	
Thoracic Lesions		4
Cancer of Lung	1	
Cancer of Chest Wall	1	
Sarcoma of Chest Wall	1	
Chronic Pneumonitis	1	
Gastrointestinal Lesions		18
Cancer of Esophagus	1	
Cancer of Stomach	4	
Cancer of Large Bowel	11	
Fibrosis of Pancreas	1	
Melanomatosis, ? Primary Colon	1	
Genitourinary Lesions		5
Cancer of Ureter	1	
Cancer of Bladder	1	
Cancer of Prostate	1	
Myoma of Bladder (Massive)	1	
Benign Prostatic Hypertrophy	1	
Gynecological Lesions		7
Cancer of Uterine Fundus	2	
Uterine Fibroids	3	
Granulosa Cell Tumor of Ovary	1	
Cancer of Vulva	1	
Soft Tissues and Bone Lesions		3
Malignant Melanoma	2	
Osteogenic Sarcoma	1	
Total		68
Malignant Tumors		57
Benign Conditions		11

Table 2 lists the types of heart disease and the functional classification. There was a correlation between functional classification and the incidence of postoperative complications inasmuch as the poorer the functional classification, the higher the percentage of postoperative pulmonary complications. However, there was no significant relationship between functional classification and cardiovascular deaths or between etiology of heart disease and cardiopulmonary morbidity and mortality. The duration of auricular fibrillation was over 5 years in 14 patients, 2 to 5 years in 3 patients, less than one year in 2, and unknown in 41 instances.

There was an increased incidence of morbidity and mortality in people with a past history of congestive heart failure, especially if such failure occurred within 8 weeks prior to admission. All 4 patients with a history of recent failure incurred cardiorespiratory complications. One patient expired on the sixth postoperative day with progressive oliguria and uremia. In 14 patients in whom congestive heart failure had occurred more than one year prior to surgery, 6 (42%) incurred postoperative cardiorespiratory complications including one death on the first postoperative day from probable cerebral embolism.

Eight patients undergoing 10 operations had had evidence of previous myocardial infarction occurring 4 months to 8 years preoperatively. There was one postoperative death in this group from uncontrolled infection. Another patient had inadequate preoperative digitalization and developed minimal congestive heart failure postoperatively, eventually dying of cardiovascular disease 13 months later. In the remainder, there were no postoperative cardiopulmonary complications. Three of 5 patients with an unequivocal history of angina pectoris undergoing 6 operative procedures developed post-

operative cardiopulmonary complications; 3 died of cardiovascular disease one, 13, and 16 months postoperatively.

Marked roentgenographic cardiac enlargement was present in 2 patients, was moderate in 24, and slight in 10. The heart was normal or borderline in size in 24 patients. Although the number of patients in each subdivision was small, no significant correlation with postoperative morbidity was evident, but 11 of the 15 patients succumbing to cardiovascular disease from one day to 3 years postoperatively, had moderate or marked cardiac enlargement preoperatively.

A variety of electrocardiographic patterns was obtained, all of which demonstrated auricular fibrillation and varying degrees of myocardial disease. The electrocardiographic findings (other than auricular fibrillation) could not be correlated with the incidence of postoperative complications.

There was a statistically significant (p less than 0.05) lower incidence of postoperative cardiopulmonary complications and postoperative tachycardia in patients who were considered to be adequately digitalized, as summarized in Table 3. Digitalization was considered to be adequate when a patient received a standard dose of digitalis for at least 24 hours preoperatively[17], had no evidence of congestive heart failure, and had an apical pulse rate preoperatively less than 90. These criteria of digitalization are inadequate as evidenced by the fact that 27% of those so classified developed tachycardia postoperatively which was not related to fever or other explicable cause except inadequate digitalization. Digitalis was not given prior to surgery to 5 patients in 6 procedures, all of whom had a preoperative ventricular rate between 60 and 88 per minute. All had mild blood pressure and pulse

TABLE 2.—PREOPERATIVE CARDIAC CLASSIFICATION OF THE 60 PATIENTS WITH CHRONIC AURICULAR FIBRILLATION UNDERGOING MAJOR SURGERY GREATER THAN ONE HOUR'S DURATION

Etiological Classification	*Number of Cases*	*Functional Classification (New York Heart Association Criteria)*				
		IB	*IIB*	*IIC*	*IIIC*	*IVC*
Hypertensive and Arteriosclerotic	26 (43%)	3	8	7	8	0
Arteriosclerotic	23 (38%)	6	12	3*	2	0
Rheumatic	9 (15%)	1	3	2	3	0
Luetic	2 (3%)	1	—	—	1	0
	60	11 (18%)	23 (38%)	12* (20%)	14 (23%)	

* Including one patient who was classified IIIC on a second operation.

TABLE 3.—CORRELATION OF ESTIMATED ADEQUACY OF DIGITALIZATION TO THE OPERATIVE CARDIOVASCULAR COMPLICATIONS, POSTOPERATIVE CARDIOPULMONARY COMPLICATIONS, POSTOPERATIVE TACHYCARDIA, AND DEATHS FROM CARDIOVASCULAR DISEASE

Adequacy of Digitalis Therapy	*No. of Operations*	*Operative Cardiovascular Complications*	*Postoperative Cardio-Respiratory Complications*	*Postoperative Tachycardia*	*Total Postoperative Complications*	*Deaths from C-V Disease*	
						Less than 12 Months Postop.	*More than 12 Months Postop.*
		No. %	*No.* %	*No.* %	*No.* %		
Inadequate	21	15 (71%)	7 (33%)	9 (42%)	16 (76%)	1	4
Adequate	55	39 (71%)	10 (18%)	15 (27%)	25 (45%)	5	5

fluctuation during the operation; 2 had postoperative cardiopulmonary complications, and 3 others had postoperative tachycardia. Seven patients had an adequate trial on quinidine preoperatively but failed to revert to a normal sinus rhythm. There were no episodes of embolic phenomena in these cases.

OPERATIVE PERIOD. The type and extent of primary disease often necessitated multiple resections and compounded procedures; therefore a concise summary of these operations was not feasible. Several of the patients had additional minor procedures, both in the hospital and as outpatients which have not been included in this series. The site of operation and the frequency of postoperative cardiovascular complications appeared to be related. Head and neck and breast operations had a very low complication rate, thoracic or abdominal procedures a higher complication rate. There seemed to be no significant correlation between the duration of operation and the incidence of postoperative cardiopulmonary complications. The usual variety of pre-

TABLE 4.—OTHER PREOPERATIVE MEDICAL DIAGNOSES

	No. of Patients	No. Postop. C-R Complic.	C-V Deaths	
			Less than 12 Mos.	More than 12 Mos.
Vascular Disease 13				
Generalized Arteriosclerosis	10	4	1	1
Remote Cerebral Thrombosis	1			
Remote Pulmonary Embolism	1			
Superior Vena Cava Syndrome	1	1		
Respiratory Tract Disease . . 14				
Senile Pulmonary Emphysema	13	4	2	2
Inactive Pulmonary Tuberculosis	1		1	
Gastrointestinal Disease . . 9				
Esophageal Diverticulum	1			
Inactive Peptic Ulcer	3			
Cirrhosis (Laennec's)	3			
Acute Cholecystitis, Cholangitis and Hepatitis	1	1		
Diverticulosis of Colon	1			1
Genitourinary System . . . 8				
Azotemia (not further classified)	6	2	3	
Benign Prostatic Hypertrophy	2	1		
Endocrine System 7				
Diabetes Mellitus	5	1		1
Nontoxic Diffuse Goiter	2			
Neuromuscular System . . . 3				
Paget's Disease	2	2		1
Severe Dorsal Kyphosis	1			
Miscellaneous 15				
Latent Syphilis (treated)	6		2	1
Obesity	5	1	1	
Chronic Alcoholism	3			
Agnogenic Pancytopenia	1			
Total	69			

There were 21 complicating concomitant diseases noted on admission and listed in Table 4. All patients with anemia received sufficient blood transfusions preoperatively to correct this deficiency. Generalized arteriosclerosis, senile pulmonary emphysema, unclassified azotemia, and obesity seemed to predispose to an increased complication and/or mortality rate, although the number of cases is too small to be statistically significant.

anesthetic medications and combinations of anesthetic agents were administered; laryngospasm or cardiac arrest did not occur. There was no relationship between preoperative medication or choice of anesthesia to operative or postoperative complications. The use of atropine in a digitalized fibrillating patient was not accompanied by an increased complication rate. Blood and fluid replacement during the operative period varied considerably, but was generally restricted to replacement of metabolic and surgical loss.

TABLE 5A.—POSTOPERATIVE SURGICAL COMPLICATIONS

(Not including 3 Postoperative Deaths)

Complication	*No.*	*End Result*
Fecal Fistula	2	Spontaneous Healing
Bladder Fistula	1	Spontaneous Healing
Bladder Dysfunction (Prolonged)	1	Spontaneous Recovery
Postoperative Hemorrhage	1	Re-exploration
Wound Slough	3	Secondary Closure
Necrosis of Colostomy Stoma, Ileus, Abscess	1	Re-exploration Healing
Partial Ileus	1	Conservative Therapy

POSTOPERATIVE PERIOD. Of 3 postoperative deaths, one patient with rheumatic heart disease class IIIC died from a probable cerebral embolism on the first postoperative day, one patient with hypertensive and arteriosclerotic heart disease class IIIC died on the sixth postoperative day with progressive oliguria and uremia, and a 66-year-old male with arteriosclerotic heart disease class IIIC, died of uncontrolled infection on the 12th postoperative day. The 57 remaining patients after 73 operations incurred the postoperative surgical and medical complications listed in Table 5a and 5b respectively. Twenty-six patients undergoing 33 operations had no postoperative complications, 4 eventually dying of cardiovascular disease, 5, 12, and 16 months postoperatively.

TABLE 5B.—POSTOPERATIVE MEDICAL COMPLICATIONS

(Not including 3 postoperative deaths)

Complication	*No.*	*End Result*
Cardiorespiratory		
Urinary Tract Infection, Septicemia, Pulmonary Embolism X3, Pericarditis	1	Eventual Recovery Under Antibiotic Therapy. Died Cancer
Pulmonary Embolism, Azotemia	1	Died C-V Disease 1 Month
Pneumonitis	2	Died C-V Disease 16 Months Died Cancer
Pulmonary Atelectasis	1	Died Cancer
Pulmonary Atelectasis and Increased Myocardial Ischemia	1	Lost
Pneumonia and Increased Myocardial Ischemia	1	Living
Postoperative Myocardial Infarction	1	Living
Postoperative Congestive Failure	5	1 Died C-V Disease 13 Months 2 Died Cancer 2 Living
Slight Cerebrovascular Accident, Congestive Failure, Increased Myocardial Ischemia	1	Pulmonary Infarction 6 Days After Discharge, Died C-V Disease 38 Months
Miscellaneous		
Diabetic Neuritis	1	Lost
Serum Hepatitis	1	Cured

Six patients developed congestive heart failure in the postoperative period, 4 of whom were inadequately digitalized according to previously specified criteria. Of the 2 patients classified as adequately digitalized, one was

overtransfused during the operative period, and the other failed to receive maintenance digitalis therapy postoperatively. All 6 patients recovered, one without the use of cardiotonics or diuretics. Two are living; 2 died of cancer; and 2 died of cardiovascular disease, 13 and 39 months postoperatively.

Of the 57 patients surviving 73 operations, 39 individuals after 50 procedures were kept on standard digitalis maintenance dosage[17]. Five patients after 7 operations received no maintenance digitalis. One patient developed minimal congestive heart failure during the hospitalization which cleared spontaneously; another was given digitalis as an outpatient for congestive failure; the remaining 3 patients have demonstrated no evidence of congestive failure during the period of observation. Two patients were apparently overdigitalized preoperatively and demonstrated bradycardia postoperatively but no other signs of digitoxicity. Their digitalis dosage was reduced until the pulse rate reached normal levels, then the usual maintenance dosage was administered.

Postoperative fluid and electrolyte administration were restricted to replacement of metabolic losses and were carefully calculated as to total amount and speed of administration. Oral feedings were started at the earliest opportunity, thereby minimizing prolonged parenteral feedings postoperatively. In this series, only 8 cases were maintained exclusively on parenteral feedings beyond the second postoperative day, and no complications, *per se*, could be attributed to the type, amount, or speed of fluid administration.

FOLLOW-UP AND END RESULTS. In addition to the 3 postoperative deaths, 27 other patients have died; 2 patients have been lost to follow-up and 28 are still surviving (Table 6). Seven patients have been lost to follow-up in regard to their cardiac status. Of the remaining 50 patients, 14 (28%) have died of cardiovascular disease, 20 (40%) have had progressive cardiac symptoms, and only 16 (32%) have had no increase in cardiac symptoms.

TABLE 6.—END RESULTS

	Postop. Deaths	*0–3 Mos.*	*4–6 Mos.*	*7–11 Mos.*	*12–23 Mos.*	*24–35 Mos.*	*36–47 Mos.*	*More than 48 Mos.*	*Total*	*Per Cent*
Died from Cardiovascular Disease	1	2	3		6	1	2		15	25
Died of Cancer with Progressive Cardiovascular Disease			1	2	1	1			5	8
Died of Cancer with no Change in Cardiovascular Disease			1	4	1			1	7	11
Died of Other Causes	2		1						3	5
Living—with Cardiac Symptoms		1	1	2	4	2	1	3	14	23
Living—without Cardiac Symptoms			2	1	3			3	9	15
Living—Cardiac Status Unknown					2	2	1		5	8
Lost					2				2	3

Discussion. In the 60 patients studied, auricular fibrillation *per se* did not appear to be responsible for any increase in morbidity or mortality with the exception of one postoperative death due to a cerebrovascular accident probably resulting from an embolus.

The incidence of auricular fibrillation has been reported to vary from 3 to 17% in different groups of patients[10,28,46], and the operative mortality for such patients, 3 to 20%[23,24,29,30,34]. The average reported survival time after the onset of auricular fibrillation is one to 5 years[2-9,11,13,14,27,29,30,32,36,41,43,45,46], although survivals up to 25 years have been recorded[2,7,11,27,30,41]. The operative mortality in this group of patients was 5% and was essentially comparable to that reported for similar age groups suffering from heart disease not associated with auricular fibrillation[21,37,40,47] or with the most favorable groups of fibrillators[23,24,29,30].

Although the number of patients in this series is too small to permit complete statistical evaluation, the data allow some general conclusions. There was no correlation between age, sex, race, type of heart disease, cardiac size, electrocardiogram, past history of myocardial infarction, choice of anesthesia, preoperative medication and duration of operation with the observed operative and postoperative complication rate. A poor functional classification of heart disease, a history of previous congestive failure, and an unequivocal history of angina pectoris may indicate an expected increase in complications. Our data are too scanty to make any statement relative to the operative risk and the duration of the auricular fibrillation. Head and neck and breast operations had a low complication rate. A history of recent congestive failure, however, was accompanied by an increase in the operative and postoperative complications. These complications occurred in all 4 patients who exhibited heart failure within 2 months of the surgical procedure.

The incidence of operative and postoperative complications was significantly greater in patients who were inadequately digitalized. The optimum amount of digitalis is not easily determined, even in the patient with auricular fibrillation. This is particularly so in the elderly so-called "slow fibrillators"[12,38] in whom control of the resting pulse rate does not necessarily signify full therapeutic digitalization. This has led us to the employment of the atropine test[19] and to an exercise response test in which the patient is considered to be receiving less than adequate doses of digitalis if his apical pulse rate rises above 100 after performing a double standard exercise[31] and fails to return to less than 90, five minutes thereafter.

It seems obvious that minor, subclinical, or even frank congestive failure will develop more rapidly in the incompletely digitalized patient. There is some evidence that the appearance of cardiac failure, in a patient with auricular fibrillation receiving maintenance doses of digitalis, requires additional amounts of the glycoside to regain full compensation[12,18,38]. This was apparent in 11 of our patients who were digitalized and followed by the usual criteria preoperatively, and yet required 2 to 15 additional cat units during the postoperative period to bring their auricular fibrillation under control.

Four of the 6 patients who developed congestive failure postoperatively were not given adequate amounts of digitalis preoperatively, providing ample evidence of the importance of complete digitalization of all patients with auricular fibrillation. It is of interest to note that the apical pulse rate was 72, 80, and 88 in 3 of these patients, and because of this, only 3 to 5 cat units of digitalis per week were given in the preoperative period. Five patients stopped digitalis after leaving the hospital, and 2 of these developed

congestive failure requiring redigitalization.

Other medical conditions which were associated with an increase in the operative and postoperative complication rate were pulmonary emphysema, azotemia, generalized arteriosclerosis, and obesity.

No correlation was found between blood and fluid replacement and the development of complications except in one instance of overtransfusion.

The deleterious effects of congestive heart failure upon cardiac output and cardiac[39], pulmonary[39], renal[22,33], and hepatic[15,26,35,42] functions are well known. Operations or anesthesia, or both, with the concomitant physiologic effects and stress reaction also produce generally similar effects on these functions[1,16,20,25,44]. Therefore, as shown by this investigation, in a fibrillating patient, especially one with reduction of cardiac reserve, not only must complete digitalization be accomplished prior to surgery, but the entire cardiovascular, pulmonary, hepatic, and renal systems must be brought into compensation and stability, if medical complications are to be minimized, and anoxemia, hypoxia, and circulatory insufficiency avoided.

Summary and Conclusions. 1) The operative mortality rate was 5% in 60 patients with cardiovascular disease associated with chronic auricular fibrillation who underwent 76 major operative procedures.

2) Cardiovascular complications occurred during the operation in 71% of the 76 procedures; cardiopulmonary complications in 22% postoperatively; the operative and postoperative course was uncomplicated in 23%.

3) No correlation was found between the operative and postoperative complication rate and the age, sex, race, type of heart disease, history of remote myocardial infarction, electrocardiographic findings, heart size, preanesthetic medication, type of anesthesia, duration of the operation, or the type and amount of parenteral blood and fluid replacement.

4) Inadequate digitalization, a history of recent congestive heart failure, angina pectoris, and a poor cardiac functional classification were associated with an increase in the complication rate.

5) There was no correlation between the incidence of operative cardiovascular complications and the development of postoperative cardiopulmonary complications.

6) Pulmonary emphysema, azotemia, generalized arteriosclerosis, and obesity were associated with an increase in the complication rate.

7) The subsequent course of the heart disease in those patients surviving the operation did not appear to be significantly altered during the period of observation.

8) Fifteen (25%) of these patients with organic heart disease associated with auricular fibrillation died of cardiovascular disease within 39 months; 11 (73%) of this group had evidence of moderate to marked cardiac enlargement preoperatively.

9) The results of this study emphasize the importance of complete digitalization with stabilization of the cardiovascular, pulmonary, hepatic, and renal systems preoperatively. The inadequacy of currently available criteria for determining the completeness of digitalization is discussed, and the routine use of the atropine and exercise tolerance tests is suggested.

10) A patient with chronic auricular fibrillation is probably no greater an operative risk than a non-fibrillating patient with equal cardiac damage, providing the patient is adquately prepared preoperatively. Careful evaluation

and meticulous care and attention to the cardiovascular, renal, hepatic, and electrolytic status during the preoperative, operative, and postoperative periods are important in reducing morbidity and mortality.

REFERENCES

1. **Bennett, H. S., Bassett, D. L.,** and **Beecher, H. K.**: J. Clin. Invest., **23,** 181, 1944.
2. **Bishop, L. F.,** and **Bishop, L. F., Jr.**: New York State J. Med., **36,** 156, 1936.
3. **Brill, I. C.**: Ann. Int. Med., **10,** 1487, 1937.
4. **Brill, I. C.,** and **Meissner, W. A.**: Ibid., **14,** 1341, 1941.
5. **Brown, M. G.**: New England Med. J., **212,** 963, 1935.
6. **Cookson, H.**: Quart. J. Med., **23,** 309, 1930.
7. **DeGraff, A. C.,** and **Lingg, C.**: Am. Heart J., **10,** 630, 1935.
8. **De la Chapelle, C., Graef, I.,** and **Rottino, A.**: Ibid., **9,** 103, 1933.
9. Iidem: Ibid., **10,** 62, 1934.
10. **Eliaser, M., Jr.,** and **Kondo, B. O.**: Arch. Int. Med., **67,** 637, 1941.
11. **Evans, W. A.**: Ann. Int. Med., **9,** 1171, 1936.
12. **Fahr, G. E.,** and **LaDue, J. S.**: Am. Heart J., **21,** 133, 1941.
13. **Flaxman, N.**: J. Am. Med. Assn., **108,** 797, 1937.
14. **Garvin, C. F.**: Am. J. Med. Sci,. **203,** 788, 1942.
15. Idem: Ibid., **205,** 515, 1943.
16. **Geller, W.,** and **Tagnon, H. J.**: Arch. Int. Med., **86,** 908, 1950.
17. **Gold, H.**: J. Am. Med. Assn., **132,** 547, 1946.
18. **Gold, H.,** and **DeGraff, A. C.**: J. Am. Med. Assn., **95,** 1237, 1930.
19. **Gold, H., Kwit, N. T., Otto, H.,** and **Fox, T.**: J. Clin. Invest., **18,** 429, 1939.
20. **Habif, D. V., Papper, E. M., Fitzpatrick, H. F., Lowrance, P., Smythe, C. McC.,** and **Bradley, S. E.**: Surgery, **30,** 241, 1951.
21. **Hannigan, C. A., Wroblewski, F., Lewis, W. H., Jr.,** and **LaDue, J. S.**: Am. J. Med. Sci., **222,** 628, 1951.
22. **Iseri, L. T., McCaughey, R. S., Alexander, L., Boyle, A. J.,** and **Myers, G. B.**: Ibid., **224,** 135, 1952.
23. **Janton, O. H., Glover, R. P.,** and **O'Neill, T. J. E.**: Am. J. Med., **12,** 621, 1952.
24. **Janton, O. H., Glover, R. P., O'Neill, T. J. E., Gregory, J. E.,** and **Froio, G. F.**: Circulation, **6,** 321, 1952.
25. **Johnson, S. R.**: Acta chir. scand., Suppl. 158, 1951.
26. **Katzin, H. M., Waller, J. V.,** and **Blumgart, H. L.**: Arch. Int. Med., **64,** 457, 1939.
27. **Kossman, C. E.,** and **Connor, C. A. R.**: Am. Heart J., **24,** 215, 1942.
28. **Laplace, L. B.**: Geriatric Medicine, Edited by E. J. Stieglitz, 2nd ed. Philadelphia, W. B. Saunders Co., 1949.
29. **Levine, S. A.**: Clinical Heart Disease, 4th Ed. Philadelphia, W. B. Saunders Co., 1951.
30. **Luten, D.,** and **Jeffreys, E. O.**: J. Am. Med. Assn., **107,** 2099, 1936.
31. **Master, A. M.**: Am. Heart J., **10,** 495, 1935.
32. **McEachern, D.,** and **Baker, B. M., Jr.**: Am. J. Med. Sci., **183,** 35, 1932.
33. **Merrill, A. J.**: J. Clin. Invest., **25,** 389, 1946.
34. **Morrison, D. R.**: Surgery, **23,** 561, 1948.
35. **Moschcowitz, E.**: Ann. Int. Med., **36,** 933, 1952.
36. **Orgain, E. S., Wolff, L.,** and **White, P. D.**: Arch. Int. Med., **57,** 493, 1936.
37. **Pfeiffer, P.,** and **LaDue, J. S.**: Am. J. Med. Sci., **217,** 369, 1949.
38. **Ray, T.,** and **LaDue, J. S.**: Am. Heart J., **30,** 335, 1945.
39. **Richards, D. W., Jr.**: Acta med. scand. Suppl., **196,** 116, 1947.
40. **Rogers, W., Wroblewski, F.,** and **LaDue, J. S.**: Circulation, **7,** 192, 1953.
41. **Rothstadt, L. E.**: Med. J. Austral., **1,** 813, 1938.
42. **Schalm, L.,** and **Hoogenboom, W. A. H.**: Am. Heart J., **44,** 571, 1952.
43. **Stroud, W. D., Laplace, L. B.,** and **Reisinger, J. A.**: Am. J. Med. Sci., **183,** 48, 1932.
44. **Volpetto, P. P., Woodbury, R. A.,** and **Hamilton, W. F.**: Am. J. Physiol., **128,** 238, 1940.
45. **Walzer, L.**: Ohio State Med. J., **36,** 281, 1940.
46. **White, P. D.**: Heart Disease, 4th ed. New York, The Macmillan Co., **1951.**
47. **Wroblewski, F.,** and **LaDue, J. S.**: J. Am. Med. Assn., **150,** 1212, 1952.

CARDIAC INVOLVEMENT IN HEMOCHROMATOSIS*

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Hemochromatosis, although a rare disease, has become well known since Trousseau originally described it[21]. Clinicians generally are aware of its clinical features, but its infrequent occurrence and varied manifestations often lead to its first recognition at the necropsy table. The condition has been reported with greater frequency in recent years, due, no doubt, to better clinical perception and improved methods of study. It is not the purpose of this discussion to indulge in a description of the disorder itself, since this has been done before in many excellent papers on the subject. Rather, the cardiac changes in this disease, which have until recently been given scant attention, will be considered.

Sheldon[18] in his classic description of the condition, makes little reference to involvement of the heart, beyond stating that it frequently contains huge amounts of iron and that some of the reported patients had died of heart failure.

Blumer and Nesbit[3] point out that for some time the French have described what they called an endocrinohepatocardiac syndrome in hemochromatosis that resulted in cardiac failure. They did not assume that the heart failure was secondary to primary involvement of the myocardium, but believed that endocrine disturbances secondary to hemochromatosis were responsible. Their patients exhibited cardiac failure at an earlier age than hemochromatosis is usually found (in fourth and fifth decades); atrophy of the testes and infantilism were present; and death occurred from cardiac failure. Little support for this hypothesis has developed elsewhere and at least it seems unlikely that this syndrome represents true cardiac failure due to hemosiderosis of the heart.

The name "bronze diabetes" was given to hemochromatosis by Hartman and Chausser in 1882 because of the association of a bronzed-appearing skin pigmentation with diabetes. This term has seemed to cling to this disease since then. Such a characterization has tended to obscure the frequency with which the disorder does occur without pigmentation or diabetes, and sometimes with overt evidences of primary cardiac disease. Such cardiac complications, when unaccompanied by diabetes or pigmentation, can become exceedingly difficult diagnostic problems. The first of the two cases reported herein well illustrates this point.

Althausen and Kerr[1], in 1933, suggested that, while up to that time cardiac failure had not been considered an important cause of death in hemochromatosis, the better control of diabetes would make it possible for many of these patients to live long enough to succumb from other complications of their disease. They felt that in the future cardiac failure might be expected to assume more importance as a cause of death. Their thoughts

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seem to have been borne out by the subsequent numerous reports of myocardial failure from hemosiderosis of the heart. It seems evident now that death from myocardial failure constitutes a considerable threat to patients who have this condition.

Excess iron storage, with the resultant picture of hemochromatosis, seems to come about by three separate mechanisms:

Endogenous, increased absorption of iron. Hitherto it has been assumed that this was the only important mechanism by which hemochromatosis was produced. A poorly understood control seems to exist in the form of an intestinal mucosal block to the absorption of much more than 1 mg. of elemental iron per day. Since, in the absence of blood loss, about 0.5 mg. of iron is lost per day, this mechanism effectively protects the normal individual from iron excess. However, severely anemic patients can absorb 5 mg. or perhaps more iron per day, and dietary and nutritional changes seem also to be able to cause a significant increase in iron uptake[5,6]. The exact mechanism of operation of the intestinal mucosal block still remains speculative and unknown. Granick[7] suggests that the concentration of ferritin in the mucosal cells might be important, but it is interesting that no evidence of a defect in ferritin formation has been demonstrated in hemochromatosis. It has been proposed that an inborn metabolic error may exist in hemochromatosis, wherein there is a greater than normal tendency for intestinal mucosal cells to reduce iron so that it can be more easily and rapidly passed on to the circulation. Recent studies indicate that some type of defect in the normal regulation of iron absorption exists, and that it may be an inherent metabolic defect is implied by the known occurrence of familial hemochromatosis, reported by Rogers[16] and others.

Exogenous iron, usually given by way of multiple transfusions, can be an important cause of hemochromatosis. Since each 500 cc. of normal blood contains roughly 250 mg. of elemental iron, it is easy to see how the receipt of many transfusions by patients who do not have blood loss, can result in enormous increases in storage iron. Excess iron acquired in this way seems first to find its way into the reticulo-endothelial cells. Eventually, however, it is slowly redistributed in the same way as absorbed iron, producing a state of hemosiderosis indistinguishable from hemochromatosis[5,13]. Schwartz and Blumenthal[17] state that not all cases of hemochromatosis following multiple transfusions have received large amounts of blood. They cite instances in which only 12 transfusions had been given over a period of 9 months. Their observations suggest that other unknown factors, such as oral iron administration, increased iron absorption in the anemic state, or nutritional factors must be operating as well.

Cardiac failure is rarely mentioned as a complication of exogenous iron excess. Case 2 seems to represent cardiac failure secondary, at least in part, to exogenous hemosiderosis.

Nutritional, dietary, or even pancreatic disorders have been suggested by Gillman and Gillman[6] as causes for increased iron accumulation. In their detailed study of malnutrition in African natives they demonstrated marked accumulation of iron in the liver and other tissues of pellagrins and in other natives, apparently well, who had subsisted on a marginal diet. Most of the pellagrins had lived on a diet consisting largely of maize. In their experimental animal studies, the Gillmans showed that such a diet was high in iron, and when fed in the presence of a low phosphorus intake, resulted in an

abnormal absorption of iron. They also found that when the pancreatic duct of cats was ligated a great increase in iron absorption took place, which indicated that in cats, at least, a deficiency of pancreatic secretion influenced the speed of iron absorption. What implication these experimental observations may have for humans is not clear. Their studies suggest the possible importance of overt or subclinical states of malnutrition in iron storage disease. Althausen *et al.*[2] believe that the changes observed by Gillman and Gillman were due to a disturbance in the dietary iron-phosphorus ratio and to a gross deficiency of protein, minerals and vitamins.

The following two case reports portray the picture of myocardial failure and death as encountered in hemochromatosis. They illustrate the disease acquired in two different ways and will serve as a basis for further discussion of the problem.

Case Reports. CASE 1. A 27-year-old male entered the United States Veterans Hospital in Portland, Oregon, for the first time October 8, 1946. He had been in excellent health until March 1944 when he first experienced easy fatigability and shortness of breath with more than usual exertion. He was in the Military Service at that time. By March, 1945, he had dyspnea on ordinary exertion. When hospitalized in 1945, he was found to have auricular fibrillation and cardiac failure. He was digitalized and improved moderately. This medication was continued until his discharge in March, 1946, after which he voluntarily stopped it. At the time of his discharge from the Service such acts as climbing stairs or walking up a moderate incline would provoke shortness of breath.

In August, 1946, swelling of his ankles and enlargement of his abdomen appeared and in the course of 5 days this swelling became very marked. He had noticed cyanosis for at least 2 months before and had had non-productive cough during the same time.

His father, mother, 3 brothers and 1 sister were living and well. There was no history of familial or chronic disease in the family.

He had had the usual childhood diseases, with no sequelae, and a tonsillectomy in June, 1942. He did not use drugs or alcohol and smoked moderately. Otherwise his past history was not significant.

Physical examination showed the patient to be well nourished and developed, markedly dyspneic and quite cyanotic about the head, neck, chest and back. His blood pressure was 120/80; pulse 120, with irregular irregularity. His temperature was normal. His skin was normal, and outside of cyanosis, showed no pigmentation or other changes. Complete examination of the head and neck was normal except for mild swelling of both eyelids, more on the right.

Examination of the chest showed evidence of fluid in the lower half of the right thorax. The cardiac impulse could not be felt but the heart seemed enlarged. Its sounds were normal. No murmurs were detected. Auricular fibrillation was present. Quite marked distention of the peripheral neck veins without significant pulsations was evident.

His abdomen was markedly distended and there was extensive edema of the skin over it. The liver could be felt four fingerbreadths below the costal margin in the midclavicular line. No other organs were palpable. The penis and scrotum were markedly swollen and there was heavy, generalized edema of the lower extremities.

Laboratory examination showed: The erythrocyte count 4,760,000; hemoglobin, 94%; leukocytes, 7,200; polymorphonuclears, 93%; small lymphocytes, 7%. Urinalysis revealed a trace of albumin, occasional hyaline casts, and an occasional leukocyte. No sugar was found. Pleural fluid from the right chest proved to be a transudate.

Digitalis was immediately administered and the following day his rhythm returned to normal. Electrocardiographic findings showed very low voltage in all complexes and mild changes not inconsistent with pericarditis.

Roentgenograms of the chest (Fig. 1) indicated diffuse enlargement of the heart, particularly to the left, and a right pleural effusion. The mediastinum did not seem to be displaced. Fluoroscopic examination confirmed the fact that the heart was considerably dilated in all chambers and poor movement was seen along the whole of the left border. Only moderate pulmonary congestion could be made out by Roentgen-ray.

The venous pressure was recorded at 170 and 188 mm. of water. Ether circulation

time was 23 seconds, the Decholin circulation time 30 seconds.

Additional laboratory studies showed the blood urea to be 16.8 mg. per 100 cc. The total plasma proteins were 7.5 gm., albumin 4.2 gm., globulin 3.3 gm. per 100 cc. Subsequent urinalyses failed to reveal any abnormalities. Repeated electrocardiograms continued to demonstrate low voltage of the QRST complexes, a slightly prolonged PR interval and a regular sinus rhythm.

Mercurial diuretics were added to his regimen. His edema disappeared and he improved greatly. His cyanosis left and the venous distention was greatly reduced but lower two-thirds of the right chest, marked cardiac enlargement with auricular fibrillation, marked hepatomegaly, moderate peripheral edema and cyanosis.

The medication previously given was continued and thoracentesis was performed. Electrocardiograms at this time exhibited the same low voltage. Auricular fibrillation was present. Further studies showed a cephalin cholesterol flocculation test of 3+, Takata-Ara test of 4+, and an icterus index of 7. Plasma proteins were still within normal limits. The venous pressure during this hospitalization rose as high as 192. The ether

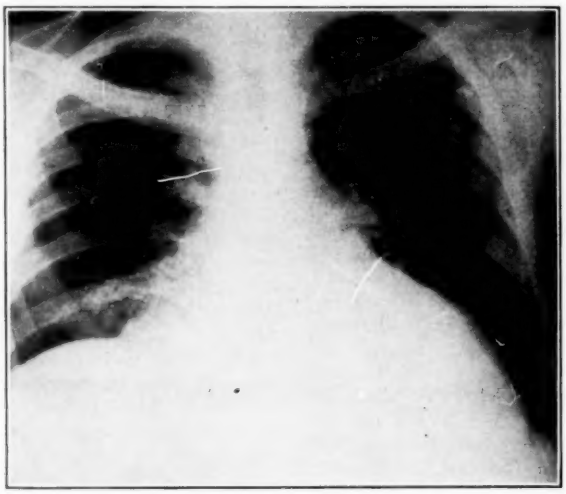

Fig. 1.—Case 1. Roentgenogram of chest taken about one month after original hospital admission. The right pleural effusion has nearly disappeared. Gross increase in the cardiac size is obvious, as are the evidences of pulmonary congestion.

not completely. For a time, serious consideration was given to the possibility of constrictive pericarditis or pericardial effusion, but observation failed to confirm these opinions. He was discharged November 23, 1946, much improved but still with a markedly enlarged heart and enlargement of the liver.

He remained at home for a month on limited activity and sat up for only 4 or 5 hours daily. Digitalis, ammonium chloride and mercurial diuretics were continued. About 2 weeks after his return to his home, his dyspnea began to increase and the ankle edema returned, forcing him to be readmitted on December 19, 1946. At this time examination again showed marked evidence of venous distention, fluid occupying the circulation time was 29 seconds, the Decholin time 32 seconds.

He improved steadily and was again discharged on February 11, 1947, with no evidence of fluid in his chest and no peripheral edema.

He was admitted to the hospital for the last time on October 16, 1947. The prescribed therapy had been followed but he continued to be short of breath and had frequent coughing spells when he would lie down or would change position. Excessive pounding and irregularity of his heart disturbed him. He often suffered from anterior chest pain of a diffuse type and would have right upper quadrant pain upon lying down. Paroxysmal nocturnal dyspnea had distressed him from

time to time. On this admission he appeared slightly icteric.

Considerable fluid was again present in the right hemithorax. The heart was quite markedly enlarged; no murmurs were heard; the apex rate was 130; the radial rate 80 to 90; auricular fibrillation was present; the blood pressure was 90/50. The abdomen contained a moderate amount of fluid and the liver was enlarged as before. There was considerable edema about the feet, ankles and lower legs.

Laboratory examination showed: 4,760,000 erythrocytes; hemoglobin, 94%; 7,200 leukocytes; polymorphonuclears 85%; small lymphocytes 15%, sedimentation rate, 34 mm. (Wintrobe). Urinalysis showed a trace of albumin, an occasional hyaline cast and leukocyte. No sugar was found.

Roentgenogram of the chest demonstrated a massive pleural effusion on the right with a shift of the mediastinum to the left. The heart still remained markedly enlarged.

Shortly after admission he complained of severe abdominal pain and became orthopneic and cyanotic. His temperature rose to 104.4° F. rectally. Subsequent to this episode, empyema appeared on the right side and a Gram-negative, non-motile, mutable colon organism was recovered from the blood. His leukocyte count rose to 13,000, his blood urea nitrogen was 20. He was treated with streptomycin and penicillin. During the next 2 weeks his temperature fell to normal and his leukocyte count to 5,200. A drainage tube was placed in the right pleural space from which foul, purulent material was drained.

Further laboratory studies showed total plasma proteins of 6.3 gm.; albumin 3.6 gm.; globulin 2.7 gm. per 100 cc.; icterus index 6; prothrombin time varying between 37 and 87%. Repeated urinalyses remained normal. His last blood count made shortly before his death was erythrocytes, 4,270,000; hemoglobin, 84%; leukocytes 4,500; polymorphonuclears 73%; small lymphocytes 27%; sedimentation rate 15 mm. (Wintrobe).

With anti-microbial therapy continued for 6 weeks, he improved. However, his electrocardiograms during this time had exhibited intraventricular block, periods of auricular flutter, and at other times, frequent ventricular premature beats. His treatment consisted of digitalis, a liberal supply of all vitamins and mercurial diuretics.

After this period of improvement, he began to retrogress and 3 weeks before his death, ankle edema, which rapidly progressed upward to involve both lower extremities, his abdomen and face, appeared. On December 27, 1947, he became extremely dyspneic, developed tachycardia of 160, a markedly diminished peripheral pulse, distended neck veins, and died the following day.

Postmortem examination was performed. Dr. Ernest J. Losli, Chief of the Laboratory Service, kindly furnished the details of this examination and a full interpretation of his findings.

At the time of postmortem no pigmentation of his skin was apparent. The *liver* was found 5 cm. below the costal margin in the right midclavicular line, 12 cm. below the costal border in the midsternal line and 12 cm. below the left costal border in the midclavicular line. The spleen was enlarged and extended below the costal border.

Complete atelectasis of the right lung was present, as well as a well-drained, chronic empyema cavity on that side. Outside of some congestion of the left lower lobe, the left lung was normal.

The *heart* was diffusely enlarged and weighed 508 gm. All heart muscle had a somewhat brownish tinge. The mitral valve admitted 3 fingers and appeared incompetent. The left ventricle was markedly trabeculated and gave the appearance of mild hypertrophy associated with marked dilatation. In the apical region of the right ventricle, there was a recent-appearing mural thrombus and in the same area of the left ventricle a mural thrombus was present which seemed somewhat organized. Cut section of the muscle in the apical region of the left ventricle showed a hyalinized appearance. The coronary ostia were patent. The coronary vessels were traced throughout their course and were noted to be patent. No infarcted areas were seen. The foramen ovale was closed. The aorta and great vessels showed no significant changes except for a very mild amount of atherosclerosis.

The *spleen* was approximately 2½ times the normal size, and two areas of wedge-shaped infarcts were found in it. It was dark red in appearance when cut.

The *liver* weighed approximately 2,200 gm. The capsule was smooth and glistening. On cut section, it had a nutmeg appearance. The biliary tract was normal.

The *pancreas* was larger and heavier than normal and cut section had a dark red color.

The left *adrenal* was somewhat enlarged. Cut sections of both adrenals showed a homogeneous, dark red appearance on the left, but a normal appearance on the right.

The *gastrointestinal tract*, from the esophagus to the rectum, showed no significant pathological alterations.

The *kidneys* were essentially normal and no obstruction or disease was found in the ureters or bladder.

Both *testes* were of normal size and consistency and were normal on cut section.

Fig. 2.—Case 1. Heart. Hematoxylin and Eosin stain. Hemosiderin deposits are extensive. Other areas showed even greater amounts than are illustrated here. Note absence of fibrosis. 175 ×.

The *thyroid* was of average size and weight and showed no changes.

Microscopic examination revealed: *Heart*: in multiple sections examined a large quantity of pigment, both within and without the myocardial fibers (Fig. 2). This pigment, with the hematoxylin and eosin stain, was yellowish, pale green, and relatively coarse. It was not limited to the paranuclear area but was found elsewhere throughout the myocardial fibers. In numerous areas the myocardial fibers had undergone complete degeneration and here only the sarcolemma sheaths were present and there appeared to be pigment within them. Pigment was found in small macrophages in the interstitial tissue. Myocardial fibers showed degenerative changes in general. The nuclei of the myofibrils were enlarged and very pleomorphic. Some of them were even staghorn in shape. The pigment was not limited to the myocardium but was also found in other areas.

The *liver* (Fig. 3) showed extensive hemosiderin deposits within the hepatic cells and there was marked cirrhosis. The pigment was also present within the cells of the biliary ducts and in the connective tissue stroma. The pancreas exhibited a marked amount of

fibrosis, with pigment deposits in large quantities in the pancreatic cells. Pigment was also found within the Islands of Langerhans and in the epithelial cells of the ducts.

Special stains revealed extensive iron deposits in the heart, pancreas and liver.

The parenchymal cells and zona glomerulosa of the *adrenals* were heavily laden with the same kind of iron pigment.

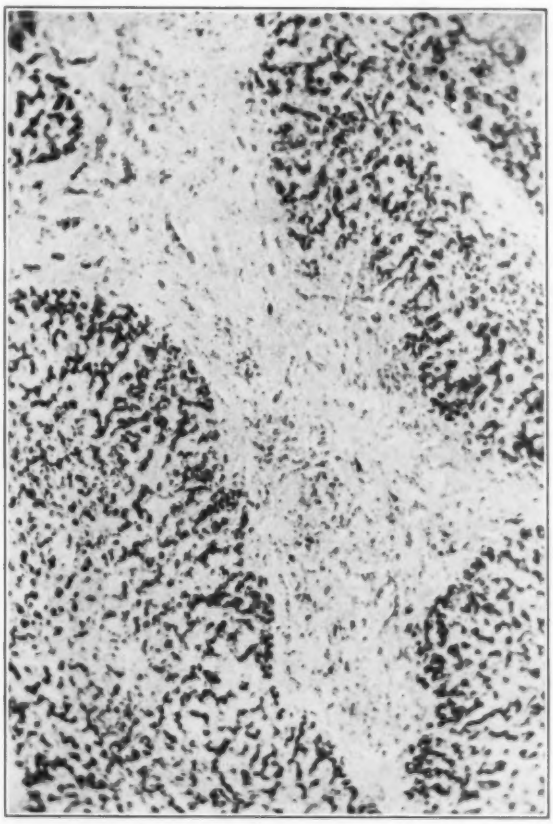

Fig. 3.—Case 1. Liver. Iron Stain. Extensive cirrhosis with heavy iron pigment concentration in the parenchymal cells. Little iron is evident in the scarred areas. Sections of the pancreas showed similar changes in the whole organ. 100 ×

Only a small amount of pigment was found in the *kidney* but a large amount was present in the spleen except in the area of infarction.

This case seems to fairly represent myocardial failure due to hemochromatosis. No other cause for the cardiac failure could be found. His youthful age is of great interest.

CASE 2. An 11-year-old, white female was admitted to the Doernbecher Children's Hospital for the last time on November 17, 1952.

She was noted to be pale at the time of birth, and at 3½ months of age, because of a rapid decline in her condition, was brought to a physician, found to have a hemoglobin of 10% and was given a transfusion of blood. From this time on the child continued to have a chronic anemia which subsequent bone marrow studies indicated was due to congenital erythrocytic hypoplasia. At no time in the course of her illness was there evidence of any deficiency of the granulocyte series. She was maintained through the years with transfusions.

The child had been normal at birth and weighed 6 pounds, 12 ounces. She was able to sit up at the age of 6 months. Nutrition

was somewhat of a problem in her case; however, she continued to develop fairly normally but was smaller than usual for her age.

Outside of the anemia, she had had no other important illnesses. At the age of 5 she had chickenpox and her liver was palpable for a time following this, but the enlargement subsided. In January, 1952, she had an illness in which her liver became enlarged briefly but receded in size.

Up to the time of her death she had received 69,570 cc. of blood by transfusion. No serious reactions had occurred with the transfusions, although brief febrile episodes were not rare following many of them.

tinued to remain large and painful, and dyspnea, as well as edema, appeared and grew worse.

Physical examination showed: Blood pressure, 95/70; pulse 120, regular; temperature normal. The patient had a dusky-gray appearance of her skin and was listless. The head and neck showed no significant abnormalities. The lungs were normal. The heart was enlarged to the left and there was a systolic murmur 2 cm. to the left of the sternum in the fifth intercostal space. The liver was enlarged to the level of the umbilicus, was quite tender but seemed smooth. The spleen could not be felt. There was marked

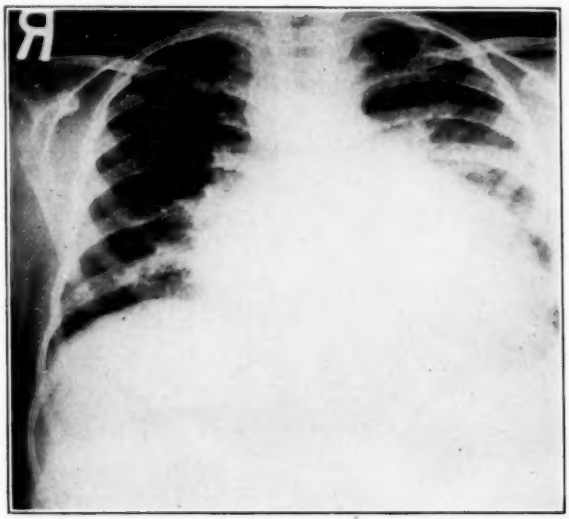

Fig. 4.—Case 2. Roentgenogram of the chest taken shortly before death. Marked cardiac enlargement and pulmonary congestion. Some of the increase in the size of the cardiac silhouette may have been due to pericardial fluid.

All manner of therapy was tried, including iron, cortisone and cobalt, but none was successful. Cortisone was last discontinued in December, 1951.

About 2 years before her death her skin began to appear somewhat slate-colored and this pigmentation slowly increased.

Numerous urinalyses had been made and at no time had any abnormalities been found.

In July, 1952, her liver began to be painful and was found to be quite enlarged. In September, swelling of the hands and ankles was noticed. In October, tachycardia was apparent and, because heart failure was felt to be present, she was treated with Mercuhydrin and digitalis. However, her liver continued to remain large and painful, and dyspnea, as well as edema, appeared and grew worse.

pitting edema of both lower extremities and in the lower back area.

Laboratory examination: The blood count showed erythrocytes 1,690,000; hemoglobin 5.3 gm.; leukocytes 4,500; polymorphonuclears 77%; small lymphocytes 14%; monocytes 9%; sedimentation rate was 40 mm. in 45 min. (Westergren); color index 1.12; volume index 1.06; saturation index 1.07; serum bilirubin 2.7 mg.; prompt direct 1.8 mg. per 100 cc. Total plasma proteins 7.2 gms.; albumin 5.2 gms.; globulin 2.0 gms. per 100 cc.

Shortly after admission she began to have severe abdominal pain without nausea or vomiting. Her pulse rate was 136 and her blood pressure became unobtainable.

A transfusion of 200 cc. of blood was given with great difficulty in the external jugular vein. Her blood pressure had risen to 80/60 by the following morning. On November 20, 1952, her blood pressure was 70mm/?; her pulse rate 120. Roentgenogram of the chest showed marked general cardiomegaly, associated with exaggeration of the hilar and vascular shadows, consistent with the edema seemed to increase. Shortly thereafter she began to expectorate foamy sputum and suddenly expired.

At necropsy there was extensive hemosiderosis of the liver, spleen, lymph nodes, skin, pancreas, adrenals and heart. The heart was dilated, exhibited moderate hypertrophy and weighed 240 gm. There was general anasarca with massive ascites. A moderate

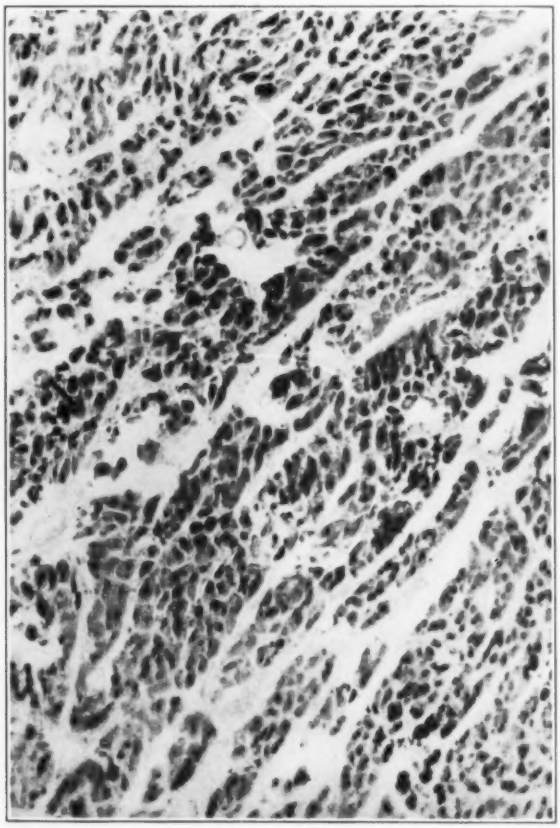

Fig. 5.—Case 2. Heart. Iron Stain. The heavy iron deposits visible in the muscle cells were widespread. No fibrosis was present. 175 ×.

the appearance of cardiac decompensation and acute passive pulmonary congestion (Fig. 4). An electrocardiogram showed runs of ventricular tachycardia interposed between brief periods of sinus rhythm. QRST complexes during the periods of sinus rhythm were somewhat widened and of very low amplitude.

She was continued on digitalis but during the day her liver became more tender and pericardial effusion, pleural effusions and pulmonary edema were present. Both adrenal cortices showed diffuse atrophy thought to be the result of prior cortisone therapy.

Microscopic examination was made by Dr. Terence Cochran of the Department of Pathology. Numerous sections of the *heart*, (Fig. 5) both from the right and left ventricles, and atria, showed considerable brown pigment, which gave a positive Prussian blue

reaction, indicating it to be hemosiderin. Most of this pigment was seen within the cytoplasm of the muscle cells. The other appreciable changes consisted of considerable variation in cell size, particularly apparent in cross section, with bizarre and variably sized cell nuclei. Striations were still evident. Although there were some fine vacuolations within the sarcoplasm of the cells, they were negative for neutral fat and might have been simply artefacts. Occasional cells showed very large square nuclei, indicating hypertrophy, and focal small cells were interpreted as being atrophied. No appreciable scarring was seen. The most striking variations in cell size were seen in the right ventricle.

The *liver* (Fig. 6) showed extensive nodular cirrhosis with broad interlacing bands of scar, predominantly periportal in distribution. Within this scar tissue there was a very heavy deposition of brown pigment, both intracellular and extracellular, which stained positive for hemosiderin by the Prussian-blue reaction. There was also extensive bile duct proliferation and some isolated, infiltrated, inflammatory cells, including granulocytes and mononuclear cells. The intervening liver parenchymal cells showed a loss of their usual relationship to any identifiable central vein. There was very little fat apparent in these cells; the cytoplasm was basophilic, with increased basophilic stippling and also showed

Fig. 6.—Case 2. Liver. Iron Stain. The relatively greater concentration of iron pigment in the Kupfer cells and regions of fibrosis, often the case in exogenous hemochromatosis, is clearly shown. The cellular content of iron was, however, high. The pancreas showed similar changes throughout all parts of the organ. 100 ×.

some iron-staining pigment. It was not nearly so marked, however, in the parenchymal cells as in the intervening scars. Most of the Kupfer cells were well outlined with hemosiderin pigment as well. At one point within the liver, there was a circumscribed, small nodule, 3 mm. in diameter, which was identified as an adenoma. The cells in this adenoma, although containing hemosiderin, showed an appreciably less amount of iron pigment as compared with the adjacent cirrhotic liver.

The *pancreas* showed considerable autolysis and widespread infiltration between the various lobules of fat. It could be appreciated, however, that there was extensive iron-stained pigment within the scar tissue, which formed a fine network throughout the lobules, as well as within the parenchymal cells and the cells of the islets.

The *kidney* showed no appreciable change, except for extensive iron-staining pigment within the tubular epithelium, particularly of the distal convoluted tubules, the loops of Henle, and probably the first portion of the collecting tubules.

Numerous sections of the *bone marrow* showed normal cellularity with normally appearing and occurring megakaryocytes, as well as adequate granulopoiesis. Areas of erythropoiesis, however, were difficult to find and undoubtedly were decreased. Occasionally there were aggregations of lymphoid cells as well. Iron stains revealed a moderate amount of Prussian-blue positive pigment within the bone marrow. It certainly was not as marked there, however, as in the other organs. Sections of the other tissues, including small and large intestine, adrenals, lymph nodes, thyroid and hypophysis all showed abundant iron-staining pigment.

This case strikingly demonstrates hemosiderosis from exogenous sources, probably exaggerated some by the effects of anemia. It could be reasonably argued that her terminal cardiac failure might have been the result of chronic anemia and high cardiac output consequent to it. However, she was not severely anemic all the time, she had no other complicating heart disease, and cardiac failure appeared suddenly after many years of management. The failure, once started, was rapidly progressive. These observations, together with the necropsy findings, would seem to make tenable the assumption this child's death was due, for the most part, to hemosiderosis of the heart. The ventricular tachycardia was not thought to be due to digitalis intoxication.

Comment. The manifestations of cardiac involvement in hemochromatosis are usually those of diffuse heart enlargement which is eventually followed by a rapidly progressive myocardial failure. Some patients have complained of exertional precordial and substernal pain but no coronary sclerosis adequate to explain this has subsequently been found[3,14]. Once myocardial failure has made its appearance, few patients live beyond 9 to 12 months, although instances have been recorded of longer life, as in Case 1 reported here.

The myocardial failure seems to be whole-heart failure, in that both sides are simultaneously involved. Right-sided failure tends to predominate. As a result, edema is a prominent finding and is often marked. The heart is found on examination to be moderately or even greatly diffusely enlarged. Murmurs are usually absent. No significant changes in blood pressure are usual, except for a general tendency toward normal or hypotensive levels.

Of considerable interest is the high incidence of arrhythmias and blocks in the reported cases. These appear to be present in a much higher ratio than is ordinarily seen in myocardial failure due to other causes, with the possible exception of coronary arteriosclerosis. Paroxysmal auricular tachycardia, auricular flutter, and auricular fibrillation include the tachycardias reported. Ventricular tachycardia seems to be exceedingly rare[1,4,8,12]. It was found in our second case as a terminal manifestation. Conduction disturbances include partial auriculoventricular block and complete auriculoventricular block with dissociation[1,14,22].

Electrocardiographic changes, outside of those produced by the arrhythmias and blocks, are not striking in degree but have been numerous. These have consisted, for the most part, of a tendency for low voltage of the QRS complex and the frequent occurrence of flattened or diphasic T waves in leads other than standard Lead III. No significant T-wave inversions and no striking deviations of the ST segment have been encountered, as far as can be determined[1,4,20]. Sinoauricular block was reported once. Premature beats of ventricular and auricular origin have been common.

The clinical diagnosis of myocardial failure due to this cause is not difficult if it occurs in association with the other classical evidences of hemochromatosis, such as cirrhosis of the liver, pigmentation of the skin, and diabetes. A steady, inexorable progress of the cardiac failure accentuates this diagnosis even more. In instances, such as our Case 1, where the cardinal corollary signs and symptoms are missing or poorly developed, the diagnosis of hemochromatosis heart disease may become extremely difficult. While the occurrence of this type of heart disease without the usual findings of hemochromatosis must be considered uncommon, nevertheless it is worthwhile to consider it in any individual who presents progressive whole-heart failure that does not respond well to treatment and for which a cause cannot with certainty be determined. In such circumstances an accessory aid, such as examination of the bone marrow for the presence of hemosiderin clumps, is of real value[5]. Determination of the serum iron and estimation of the degree of saturation of the iron-carrying protein, siderophylin, is, of course, also helpful. In hemochromatosis the serum and siderophylin almost invariably will be found saturated with iron[7]. Liver biopsy demonstration is naturally one of the strongest evidences of the existence of this disease, but may be hazardous in the presence of myocardial failure with hepatic congestion.

Pathological study of the heart in hemochromatosis, while revealing many changes, fails to explain adequately the cause of myocardial failure. No coronary artery disease of note has been described. The heart muscle uniformly has a brownish color and the total heart mass is very often increased in amount, sometimes considerably. Evidences of mild hypertrophy are often seen, and dilatation of all the cardiac chambers, more particularly the right, is the rule. Mural thrombi, without evidences of underlying myocardial infarction, have been reported from time to time in either or both ventricles, and clots have also been described in the auricular appendages. Histologically, a variety of changes are seen. Most outstanding are the deposits of hemosiderin pigment in the heart muscle fibers. The pigment in them is clustered most heavily about the nuclei in a polar distribution that extends from the nuclei in a linear manner toward the ends of the cells for varying distances. All phases of degenerative changes in the cells may be seen: swelling, hydropic changes, atrophy, splitting and fissuring of the muscle fibrils, loss of the muscle striations, pyknosis and karyorrhexis. Some cells show complete loss of sarcoplasm with only the sarcolemma remaining and enclosing a mass of granules of hemosiderin. This change was seen prominently in Case 1[1,3,8,11,12]. Fatty degeneration of the muscle has been described[14].

No correlation can be made between the intensity of the hemosiderosis and the occurrence of fibrosis. Some cases that have had severe failure show almost no fibrosis. Others have exhibited

myofibrosis, occasionally of severe degree[3,8,11]. Many observers have described hemosiderin granules in histiocytes, mononuclear cells, and in areas of definite fibrosis. However, usually little hemosiderin is found outside the muscle cells. In some of the hearts containing the heaviest iron deposition, fibrosis was minimal or absent. Areas of fibrosis of a patchy type have been described. These have not been due to vascular injury, as far as could be determined. Occasionally interstitial edema is noted[12]. Slight thickening of the pericardium has been found occasionally but never to an important degree. No adequate studies of the conduction bundles have been made.

Some hearts show abnormally large amounts of hemosiderin and yet have not undergone failure, in contrast to some which contain lesser amounts of hemosiderin and have been in advanced failure. Such a circumstance may be in part, the result of the factor of time, since some patients with advanced hemochromatosis die of hemorrhage, liver insufficiency or other complications before they may have had time to develop the myocardial failure that would have appeared later.

It seems likely that the simple storage of iron in cardiac muscle in the torm of ferritin and hemosiderin does not, in itself, cause irritation, subsequent degeneration of the fibers and replacement fibrosis[7]. In the light of the failure of anatomic changes adequately to explain the myocardial failure, some other cause, such as a derangement of cellular physiology and chemistry due to an excess of iron, might be at the root of the cardiac weakness.

Ferritin is a protein substance which contains within its structure clusters of polymerized masses of ferric hydroxide. It exists in normal heart muscle in small amounts or not at all. In hemochromatosis considerable concentrations are found. Hemosiderin is made up of large clusters of iron hydroxide groups which are mixed with some type of protein. Recent evidence[19] indicates that it may be composed of sizable aggregates of ferritin which tend to accumulate when iron stores are excessive. These aggregates become large enough to be visible microscopically, can be stained for iron and may contain as much as 35% by weight of the metal[7]. Hemosiderin iron is available for use, as is ferritin iron. However, when present in such large amounts as to interfere with cell function its mobilization is impaired[5,19].

Large amounts of hemofuscin and melanin are characteristically found in hemochromatosis, but there is no evidence that either of these pigments plays any part in the disturbance of the heart or other structures.

Racker and Krimsky[15] demonstrated with brain homogenates that exceedingly small amounts of ferrous sulfate would partially inhibit the enzyme glyceraldehyde phosphate dehydrogenase. This enzyme acts rather far down in the glycolytic cycle, but its inhibition would decrease the formation of the high-energy adenosine triphosphate (ATP). ATP is necessary for the proper phosphorylation of glucose. These investigators found that some effect, presumed to be due to a decrease in ATP, reduced the formation of fructose-1-6-diphosphate. Inhibition along this earlier part of the chain of reactions would further limit the amount of ATP formed. If it can be presumed that excess iron stores in heart muscle have a similar effect upon the glycolytic cycle in its cells, a profound effect upon heart muscle metabolism would result. It seems reasonable, too, that insoluble iron phosphate compounds may be precipitated from phosphate-containing proteins in the sarcoplasm, the nucleo-proteins of the

nucleus and from ATP in the presence of excess cellular iron. No proof of such changes exists at present. Certainly, the swelling, hydropic degeneration, atrophy, vacuolization, fibrillation and fatty changes in the heart muscle cells suggest some kind of biochemical disturbance.

Treatment of these cases is unsatisfactory. The usual measures applied to the treatment of congestive heart failure with edema are effective to one degree or another for a while, but eventually, as was true in both our cases, such measures invariably fail. The effects of the removal of iron stores by repeated bleeding is under study at the present time by numerous investigators[5]. Large quantities of iron can be removed this way but it is uncertain at present as to what effect this will have on the over-all disease. Such a form of therapy, which requires a prolonged period for any definitive effect, would hardly be applicable in most of the cases of heart failure due to hemochromatosis because the period of failure is of such short duration. Recognition of the possibility of heart injury before the state of irrevocable tissue damage might make constructive results from this therapy possible, but final judgment of this approach must await further investigation[5,9,10].

Summary and Conclusions. The mechanism of excess iron storage in the body is reviewed.

Three reasons for such excess iron stores have been advanced: *endogenous* because of increased intestinal absorption due to unknown causes; *exogenous* by way of multiple transfusions; and *nutritional or dietary* disturbances which may enhance iron absorption.

Clinical and pathological features of the whole-heart failure seen in hemochromatosis are discussed. Two cases are presented that represent hemosiderotic heart disease acquired by endogenous and exogenous mechanisms.

Simple irritative injury to cardiac muscle cells by hemosiderin deposits seems inadequate as an explanation for cardiac failure. Biochemical changes in important enzyme systems and the destruction of phosphate-containing protein substances in the sarcoplasm and nucleus by the excess iron may be a cause for the myocardial failure.

Treatment of established heart failure due to hemosiderosis is usually unfruitful. Repeated bleeding to remove excess iron stores may be a way to reduce the severity of the changes found in hemochromatosis.

REFERENCES

1. **Althausen, T. L.,** and **Kerr, W. J.:** Endocrinology, **17,** 621, 1933.
2. **Althausen, T. L., Doig, R. K., Weiden, S., Motteram, R., Turner, C. N.,** and **Moore, A.:** Arch. Int. Med., **88,** 553, 1951.
3. **Blumer, G.,** and **Nesbit, R. R.:** New England J. Med., **218,** 295, 1938.
4. **Bothwell, T. H., Van Lingen, B., Alper, T.,** and **du Preez, M. L.:** Am. Heart J., **43,** 333, 1952.
5. **Finch, C. A., Hegsted, M., Kinney, T. D., Thomas, E. D., Rath, C. E., Haskins, D., Finch, S.,** and **Fluharty, R. G.:** Blood, **5,** 983, 1950.
6. **Gillman, J.,** and **Gillman, T.:** Perspectives in Human Malnutrition. New York, Grune & Stratton, 1951.
7. **Granick, S.:** Bull. New York Acad. Med., **25,** 403, 1949.
8. **Griffin, W. R., Nelson, H. G.,** and **Seal, J. R.:** Am. Heart J., **39,** 904, 1950.
9. **Haskins, D., Stevens, A. R., Jr., Finch, S.,** and **Finch, C. A.:** J. Clin. Investig., **31,** 543, 1952.

10. **Houston, J. C.**: Lancet, **1**, 766, 1953.
11. **Keschner, H. W.**: South. Med. J., **44**, 927, 1951.
12. **Levin, E. B.**, and **Golum, A.**: Am. Heart J., **45**, 277, 1953.
13. **Norris, R. P.**, and **McEwen, F. I.**: J. Am. Med. Assn., **143**, 740, 1950.
14. **Petit, D. W.**: Am. Heart J., **29**, 253, 1945.
15. **Racker, E.**, and **Krimsky, I.**: J. Biol. Chem., **173**, 519, 1948.
16. **Rogers, W. F., Jr.**: Am. J. Med. Sci., **220**, 530, 1950.
17. **Schwartz, S. O.**, and **Blumenthal, L. A.**: Blood, **3**, 617, 1948.
18. **Sheldon, J. H.**: Haemochromatosis, London, Oxford University Press, 1935.
19. **Shoden, A., Gabrio, B. W.**, and **Finch, C. A.**: J. Biol. Chem., **204**, 823, 1953.
20. **Swan, W. G. A.**, and **Dewar, H. A.**: Brit. Heart J., **14**, 117, 1952.
21. **Trousseau, A.**: Clinical Medicine, 1868-1872, New Sydenham Society, Vol. 3, pp. 500-502.
22. **Tucker, H. St. G., Jr., Moss, L. F.**, and **Williams, J. P.**: Am. Heart J., **35**, 993, 1948.

AN INTERESTING EXPERIENCE WITH TRANSMISSION OF HOMOLOGOUS SERUM JAUNDICE

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The hazard of homologous serum jaundice developing in recipients of blood transfusions, one of the major and as yet unsolved problems in hemotherapy, continues to cause great concern to all workers in the field. None of the screening procedures, as represented by inquiry into medical history and clinical examination of prospective donors and by laboratory tests on pilot specimens of blood, has been found to eliminate reliably carriers of the virus of hepatitis. Moreover, there is justified suspicion that rejection of donors, or exclusion of units of blood, on the basis of some of these screening procedures may needlessly exclude safe blood from use for transfusion. Finally, in cases where homologous serum jaundice develops in a patient following administration of whole blood or of a blood fraction, it is only rarely possible, even in retrospect, to identify positively the source of the virus in the form of a specific donor. This state of affairs justifies the following brief report.

Case Report. A 48-year-old man, hospitalized for a retroperitoneal abscess, received prior to operation one unit of whole blood on November 1, 1952. Recipient and donor were of group B, Rh-positive, with crossmatching tests demonstrating compatibility. No untoward effects followed the transfusion. The patient made a good recovery after appropriate surgical and medical treatment, which did not include any more transfusions or other blood fractions. He was discharged on November 23, 1952.

On February 20, 1953, the patient was readmitted with a history of anorexia, malaise, and gradually developing jaundice during the previous week. History, physical examination, and laboratory findings (serum bilirubin: direct, 1.9 mg.; total, 3.5 mg./100 cc.; urine: bilirubin present; cephalin flocculation, 4+; thymol turbidity, 17 units) agreed in supporting the diagnosis of viral hepatitis. In view of the fact that a blood transfusion had preceded onset of symptoms by 105 days, and in view of the absence of any exposure of the patient to any known case of epidemic hepatitis, the diagnosis of homologous serum jaundice was suggested. Clinical and laboratory findings gradually returned to normal, and the patient was discharged on March 10, 1953, as recovered.

Review of the record of the donor whose blood was given to the patient gave the following information: he was a 43-year-old man donating blood for the first time in his life. His medical history failed to disclose any relevant data, and, in particular, on being questioned the donor denied ever having had jaundice, or any symptoms referable to liver disease, or having been in contact with any person suffering from such illness. His pulse, blood pressure, temperature, respiration, weight, and hemoglobin were within normal limits. Serologic tests for syphilis were negative. The only laboratory test referable to hepatic function done on the pilot specimen was total serum bilirubin, which was also found to be in the normal range (less than 1.2 mg./100 cc). The blood donation was made on October 19, 1952.

When the diagnosis of homologous serum jaundice was suspected in the recipient of the blood of this donor, attempts were made to recall the donor who lived out-of-town. The donor cooperated in sending in the name

of his private physician,* who at our request, forwarded on March 28, 1953, a blood specimen of the donor and the following history: "On October 27, 1952, (8 days after donation), Mr. B. (the donor) developed chills, fever (103°), general malaise, headache, and backache. A mild jaundice appeared on October 30, lasting about one week. His younger daughter developed within one week similar symptoms and jaundice. Mrs. B. and the oldest daughter were given injections of immune serum globulin, and remained well." At the time of this report the donor had completely recovered and was free of any subjective or objective anomalous findings. Tests done on the blood specimen of March 28, 1953, gave the following results: total serum bilirubin, 0.5 mg./100 cc.; cephalin flocculation test, negative; thymol turbidity, 3.3 units.

Summary and Conclusions. The reported observations indicate that we were dealing with development of homologous serum jaundice in a patient transfused with blood from a donor who was in the incubation period of infectious (viral) hepatitis. Attention may be called to the following implications to be drawn from these observations: (1) serum bilirubin of the donor was within normal limits 8 days before onset of viral hepatitis, as well as approximately 5 months later. (2) With 4 units representing the upper limit of norm of thymol turbidity according to the method used, this test was in the upper normal range in a patient approximately 5 months after having had infectious hepatitis; regrettably, the test had not been done on a specimen obtained 8 days before onset of disease. (3) In this particular incident of a donor giving blood while in the incubation period of hepatitis, the unit of blood was not used until a few days after onset of symptoms in the donor. For this reason, donors should be urged to inform the bank where they gave blood of any illness occurring within 3 weeks after donation. By the same token, when hepatitis is diagnosed or suspected in a patient, it may be well to inquire whether the patient recently donated blood, and if so, one should notify the blood bank of the illness. In this manner potentially dangerous blood may be excluded from hemotherapeutic use in a few instances. (4) While the exact relationship between the viruses of infectious hepatitis (IH or hepatitis type A) and of homologous serum jaundice (SH or hepatitis type B) is not known, Stokes[1] has presented ample evidence to support the assumption of nonidentity of the 2 viruses. The mode of transmission and the incubation period in the recipient of the blood transfusion suggested presence of hepatitis type B. Since both father (donor) and daughter showed symptoms of disease within a short period of time, both might have been infected with virus A. Thus another possibility to be considered is that the blood donor was a "carrier" of hepatitis virus B and had a superimposed epidemic hepatitis due to hepatitis virus A.

While it is obvious that no generalizations are permissible on the basis of a single incident as observed by us, we felt justified in making this report, and would like to urge other workers to do likewise in similar circumstances, because it is unlikely that large series of such cases can be collected by one investigator. Hence experiences, which may be important in contributing to our understanding of the nature and transmission of homologous serum jaundice, most likely will have to be gathered collectively rather than individually.

*Thanks for his helpful cooperation are herewith expressed to Dr. Clifford W. Fredberg, Rockford, Illinois.

REFERENCE

Stokes, J., Jr.: Am. J. Med. Sci., **225**, 349, 1953.

USE OF CHLORPROMAZINE IN CHRONIC ALCOHOLICS*

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One of the pressing problems in the treatment of any alcoholic is the adequate control of the withdrawal symptoms of tremulousness, excitement, and agitation accompanying any present day therapy. In utilizing disulfram therapy, it is necessary that the patient be without alcohol for a period of 6 days prior[3] to the initial administration of this drug, if a disulfram reaction is to be avoided. This period of sobriety has been a hazard for many of those embarking upon the disulfram program because no medication previously available would control the psychomotor agitations as effectively as "one more drink".

It is a common experience among those who treat patients with disulfram that after varying periods of sobriety patients will often stop taking the drug and go on a planned "bender". Usually after several days of debauchery, these people want to quit drinking but are unable to do so because of the nagging and craving for alcohol. Moreover, they are very fearful of the symptoms of tremulousness, excitement, and agitation attendant to any "drying out" procedure mandatory before reinstitution of the disulfram program.

Psychomotor agitation is a phenomenon frequently observed in patients following moderate or severe inebriation. This can be most distressing, not only to the patient himself, but to the family, the doctor, and hospital ward personnel, because of the inability to control this agitation adequately. These symptoms may vary with the individuals, depending on the length and severity of the intoxication.

Withdrawal symptoms may take the form of any one of the following paterns: boisterousness, bravado, profanity, incoherent speech, clumsiness, sadness, elation, tremulousness to a point where the patient may not be able to sit quietly, insomnia, changes in personality, hallucinations, marked fear, and sometimes frank psychotic episodes. Patients may become combative and abusive to others around them, or so violent as to require commitment for psychiatric care for their own protection, as well as that of personnel. Others may exhibit profound automatism. Death from acute intoxication is a real possibility. The agitation gradually decreases over a period of days until the only complaint the patient has is a sensation of "butterflies or crawling

*Chlorpromazine, supplied as "Thorazine" by Smith, Kline & French Laboratories, Philadelphia, Pa., was developed in France by Rhone-Poulenc, who market it abroad and in Canada as "Largactil".

things in the stomach". Meanwhile, the patient has experienced an emotionally distressful period. Sedation with paraldehyde, barbiturates, and chloral hydrate has been used in the past to control this excitement. Usually, these drugs have proved only moderately successful in the average case, and in delirium tremens or severe psychomotor agitation have been woefully inadequate. In our experience, none of the commonly employed measures such as hydration with 10% dextrose and water, insulin, ACTH, Cortisone, adrenal cortical extract, or thiamine has been of outstanding value in combating post-alcoholic psychomotor agitation.

During the past year, we have studied the antiemetic drug chlorpromazine[2] and found it to be effective in preventing nausea and vomiting produced by a wide variety of drugs and clinical conditions. Since it is well known that nausea and vomiting are commonly produced by the ingestion of disulfram in the presence of alcohol[1], we decided to evaluate the effectiveness of chlorpromazine in suppressing these symptoms. In addition to its antiemetic effect, it has been observed that this compound also exhibited a mild sedative effect and has many of the properties of the antihistamine compounds such as diphenhydramine. It was felt that this feature might prove somewhat useful in reducing the psychomotor excitement. While this study was in progress, we had the opportunity of conversing with Dr. Martensen-Larsen, who has treated a number of acute and chronic alcoholics with disulfram, diphenhydramine (Benadryl), and sodium chloride[5]. He noted some suppression of nausea and vomiting with this regimen.

Material and Method. We have treated a total of 60 patients suffering with acute or chronic alcoholism, incipient and frank delirium tremens who presented themselves to the emergency ward or alcoholic clinic for help. Each person was given a complete physical examination, including electrocardiogram when possible, prior to the institution of any therapy. About half of the patients treated had previously been followed in the alcoholic clinic and results of extensive work-ups, including chest roentgenograms, electrocardiograms, routine laboratory examinations, bromsulfalein tests, and psychometric examinations were available.

Irrespective of the quantity of liquor consumed, patients were given simultaneously 100 mg. of chlorpromazine and 500 mg. of disulfram, by mouth. within 6 hours, chlorpromazine 50 mg. was repeated. Twenty-four hours later, 500 mg. disulfram and 50 mg. chlorpromazine were administered. Forty-eight hours following initial therapy, 500 mg. of disulfram and 25 mg. of chlorpromazine were given. Thereafter, for one week 500 mg. of disulfram was administered daily. The dosage of disulfram was then adjusted to the patient tolerance, usually 0.25 or 0.5 gm. daily. If the patient was vomiting, 50 mg. of chlorpromazine was given intramuscularly and, with suppression of the vomiting, oral medication was begun according to the above schedule, except that the first oral dose was 50 mg. rather than 100 mg. chlorpromazine. In addition to the above therapy, in the more severely dehydrated patient some attempt was made to overcome this by intravenous dextrose and water.

Initially, patients were observed for 24 to 48 hours on the emergency ward. However, since no untoward effects were noted in these cases of frank delirium tremens, the medication schedule was carefully taught to a responsible person, wife or friend, who accompanied the patient, and the en-

tire program was carried out on an outpatient basis.

Results. It was immediately apparent that chlorpromazine was effective in suppressing the nausea and vomiting produced by the disulfram-alcohol reaction. Of much greater interest, however, was the effect of this drug combination in preventing the usual post-alcoholic psychomotor agitation accompanying withdrawal. Within an hour or so most patients tended to become drowsy, quite calm, and some actually went to sleep. The sleep was described as refreshing and usually the most restful these persons had been able to obtain in weeks. This sleep period usually lasted 10 to 12 hours. Most patients had to be awakened for the repeat dose of chlorpromazine. Within 24 hours, patients were hungry, and they were able to take solid foods. Some tremulousness was still apparent at the end of this 24 hour period, but restful sleep could be secured at any time during the entire withdrawal period. Patients in several instances were able to return to work within 72 hours without having experienced the "jitters", tremulousness, or "butterfly" sensation so common during the withdrawal stage.

Controls were studied using chlorpromazine alone. Patients who had been drinking for a period of days were given chlorpromazine in a schedule as described above. In addition, a series of 6 patients were given chlorpromazine intramuscularly in similar amounts to avoid any possible absorption failure. In none of these patients were results as satisfactory as with the combination of drugs. Patients would continue to drink. The agitation was, at best, only partly relieved, and in only 2 cases were the patients able to sleep.

Controls using disulfram alone were not tested for it is known that disulfram administered in the presence of alcohol produces a severe physiological and psychological series of reactions. The nausea and vomiting attendant with this drug combination is the basis of conditioned reflex therapy[4].

Nausea and vomiting are variously reported to accompany disulfram-ethanol reaction in 60% to 85% of cases treated. On the other hand, there are some persons who do not get a disulfram reaction with small amounts of drug and liquor, but, at best, these comprise only 1% to 2% of patients. We feel that the number of patients in this series is sufficiently large to eliminate this possibility. However, 2 patients who were being treated on an ambulatory basis for acute and chronic alcoholism, and incipient delirium tremens omitted the chlorpromazine prescribed, taking only the disulfram as outlined above. Both of these patients on consuming 0.5 gm. disulfram experienced a mild disulfram reaction. Neither stopped drinking and again took 0.5 gm. disulfram the next morning. Following a total dose of 1.0 gm. within 12 hours, a more severe form of disulfram-ethanol reaction developed. Nausea and vomiting, agitation, tremulousness, flushing of facies, and palpitation were noted. Chlorpromazine was administered to these individuals, 100 mg. intramuscularly, with prompt disappearance of symptoms. The mild hypotensive episode in one of these patients disappeared soon after intramuscular injection.

Conclusions. 1. We have presented a method for treating chronic alcoholics which eliminates the need to wait for "drying out" prior to the administration of disulfram.

2. Disulfram and chlorpromazine, when administered together in adequate dosage to the inebriated alcoholic, produces a tranquilized state

more effectively than with any current method of sedation.

3. No untoward side effects have been noted in the treatment of these 60 alcoholic patients. Nausea, vomiting, and hypotensive episodes have not been noted in our experience with this combination of drugs.

4. Chronic alcoholics treated in the described manner do not suffer with the usual postalcoholic psychomotor agitation.

REFERENCES

1. **Bell, R. G.**, and **Smith, H. W.**: Canad. Med. Assn. J., **60**, 286, 1949.
2. **Friend, D. G.**, and **Cummins, J. F.**: J. Am. Med. Assn., **153**, 480, 1953.
3. **Glud, E.**: Quart. J. Studies on Alcohol, **10**, 185, 1949.
4. **Larimer, R. C.**: J. Am. Med. Assn., **150**, 79, 1952.
5. **Martensen-Larsen, O.**: Quart. J. Studies on Alcohol, **14**, 406, 1953.

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THE PRESENT STATUS OF GAMMA GLOBULIN IN THE PREVENTION OF PARALYTIC POLIOMYELITIS

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MUCH has been written lately about the use of gamma globulin in combating poliomyelitis. Large amounts of money and energy have been spent and are to be spent on this endeavor. It may be useful to bring together the available information in order to find out where we stand and where we ought to go from here.

First, it should be clearly recognized that gamma globulin is completely valueless in the *treatment* of poliomyelitis. Bahlke and Perkins gave large amounts of gamma globulin to 56 patients in the pre-paralytic stage. Fifty-five patients in a similar stage served as untreated controls. No benefit was observed in the treated group[1].

The potential value of gamma globulin in the prophylaxis of poliomyelitis is predicated on the following observations:

1) The serum of most adults in this country today contains antibodies to one or more types of poliomyelitis virus. The antibodies develop as a result of infection which is usually inapparent or unrecognized.

2) Gamma globulin, as prepared by the American Red Cross, is derived from pools of plasma furnished by many thousands of donors. Enders found that its antibody potency is fairly uniform from lot to lot, and, in respect to Type 2 poliomyelitis antibody, the concentration was 10 to 16 times greater than that of the original plasma[9]. It contains antibodies to the 3 known types of poliomyelitis virus

in approximately equal concentration[3,27].

3) Gamma globulin has been shown to be capable of conferring passive protection to experimental animals subsequently challenged with poliomyelitis viruses.

These observations, in general, formed the basis for proceeding with large-scale field tests in man. Before discussing the results of those tests, it may be helpful to examine the background in more detail.

1) Most of the available information on the distribution of antibody in human serum concerns antibody to Type 2 (Lansing) poliomyelitis virus. It has been shown that in this country today Type 1 is the important epidemic strain. Type 3 is next in importance. Tests for antibodies to Types 1 and 3 have only recently been made practicable by the tissue culture techniques developed by Enders, Weller and Robbins[10,11,22]. Limited observations show that in people 18 years of age and older Type 1 antibody is present in about 80%, Type 3 in about 70%, and Type 2 in about 65%. On the other hand, antibody for all 3 types in one person was found in only 50%[24].

2) Although it is generally held that gamma globulin contains the 3 types of antibody, it is important that the 2 assays that showed this were made on gamma globulin prepared from enormous pools of plasma collected by the American Red Cross from all over the country[3,27]. Youngner reported only recently the results of antibody assay on the very lots of gamma globulin used by Hammon and associates in the human field trials. These lots contained appreciable amounts of all 3 types of poliomyelitis antibody[27]. Available information is scant concerning the amount and variability of antibody in different lots of gamma globulin prepared commercially from pools of plasma which are comparatively small in number and geographically restricted.

3) Until recently most experiments showing protection against poliomyelitis in animals given gamma globulin were concerned only with large amounts of gamma globulin: amounts which would be impractical to give human beings on a weight-for-weight basis[7]. Within the past 2 years, however, studies have been reported in which some protection was shown in animals receiving small quantities of gamma globulin (0.1 to 0.2 cc. per pound) and tested with virus introduced by peripheral routes. Hammon, Cheever, and Sather[15] carried out experiments with infant mice which are susceptible to a strain (MEFI) of Type 2 virus injected intra-abdominally. Gamma globulin from human plasma was given intramuscularly in varying dosages 24 hours before virus. Combining the results of 3 experiments in which 0.1 cc. of gamma globulin per pound was given the mortality was 50/167 or 30% in the treated mice as compared to 190/256 or 74% in the controls. Mice given gamma globulin in dosage less than 0.1 cc. per pound were not protected. Bodian[5] tested the effects of 0.01 cc. and of 0.1 cc. of gamma globulin per kilogram in young cynomolgus monkeys fed Type 1 virus immediately after the prophylactic injection. Of 10 monkeys given the smaller dose, 3 developed paralytic poliomyelitis. Five of 10 control monkeys became paralyzed. None of 8 monkeys which received 0.1 cc. per kilogram came down with paralysis, while 4 of 9 controls did. The numbers are small but the results with 0.1 cc. per kilogram dose suggest a protective effect.

Field trials to determine the effect of gamma globulin in preventing paralytic poliomyelitis in man were carried out in 1951 and 1952 by Hammon, Coriell,

Wehrle, and Stokes[13,14,16-19]. This study was carefully planned and strictly controlled in order to minimize the influence of bias or chance. Approximately 55,000 children in 3 epidemic areas were inoculated, half with gamma globulin and half with gelatin. No one knew at the time which material was being injected into which child. By the same token, the final clinical evaluation was made and recorded by examiners who had no knowledge as to which children had received gamma globulin. The dose, arbitrarily selected for practical reasons, averaged 0.14 cc. per pound of body weight. The results are well-known and will not be described in detail here. To summarize briefly, 104 paralytic cases developed in all the inoculated groups. Seventy-three occurred in the controls injected with gelatin and 31 in the groups given gamma globulin. This outcome could have happened by chance alone less than once in a thousand times. During the period from the second to the fifth weeks inclusive, a total of 46 paralyzed cases developed in the inoculated groups, 39 in the gelatin group and 7 in the gamma globulin group. This result is also highly significant. During the first week and after the fifth week the observed differences were probably not significant. The authors claim, however, that in the week following injection, even though the disease was not prevented, some modification of paralysis was observed in those given gamma globulin. Thus a total of 28 children in both groups developed paralysis within one week of injection; of 12 children given gamma globulin, 6 recovered completely while only 1 of 16 in the gelatin group did so.

When this study was in the planning stage, considerable doubt was raised concerning whether or not to include an inoculated control group. The objection to such a group stemmed from the possibility that the injection of even inert material such as gelatin might increase the incidence of paralysis. There is little doubt that previous work has shown a correlation between immunizing injections and the site of paralysis in the injected limb. There is conflicting evidence, however, on the question of whether or not the incidence of paralysis is increased. In any event, the final decision was to inject a control group with gelatin. Uninoculated children who did not attend the clinics, although not strictly comparable, provided another control group. The question has been raised, in evaluating the results, of whether or not the injections of gelatin provoked paralysis. The data suggest that one situation where this might have occurred was in Texas during the first 2 weeks after closing the clinics. The paralytic case rate was higher in those injected with gelatin than in those not inoculated: 0.724 and 0.287 per thousand, respectively. During the third and fourth weeks after closing the clinics, the rates in the 2 groups were 0.121 and 0.199, respectively, and thereafter the rates were about even. The authors state that in the Texas area the reporting of cases among uninoculated children was obviously incomplete which would tend to lower the rate artificially for this group. Sabin, in a critical analysis of the data, points out that if under-reporting were responsible for the difference observed in the first 2 weeks, one would expect a higher rate in the gelatin group to persist during the entire period after the closing of the clinics[23]. This did not occur. The rates in the subsequent weeks in the uninoculated children were either higher or equivalent to those in the gelatin group. Hammon and co-workers explain this shift as "due to probable increased cooperation in reporting cases in the groups that did not receive injections."

Be that as it may, Hammon and his associates emphasize that the most conspicuous finding in other studies correlating paralytic poliomyelitis and inoculations has been the *localization* of paralysis in the injected limb. In their study, all injections were given in the right buttock. Careful muscle examination of those with residual paralysis after 60 days showed the incidence of right hip and right leg involvement to be virtually the same in the gelatin-inoculated group and in those who received no inoculation. It seems to this reviewer that the absence of localization of paralysis in the injected leg, when coupled with the existence of incomplete reporting in the uninoculated group at least during the first 2 weeks, make it unlikely that gelatin provoked a significant amount of paralysis. Evidence from experiments in the laboratory (reported after the field trials) bearing on this question has also been conflicting. Melnick and Ledinko[21] failed to show an association between injection and paralysis in monkeys. Bodian, on the other hand, reported a "suggestive increase" in the paralytic rate of monkeys inoculated with gelatin intramuscularly and poliomyelitis virus intracardially[4].

If one disregards the gelatin controls and compares only the gamma globulin and uninoculated groups the differences are statistically significant in every area except Texas. The results in Iowa, the scene of an unusually severe epidemic, showed a marked difference; attack rates of the uninoculated and gamma globulin groups were 5.3 and 1.7 per thousand, respectively. Thus it appears that under the conditions of this test, with large numbers of children receiving those lots of gamma globulin at a favorable moment in a severe outbreak, there is no doubt as to its effectiveness. Whether or not the experience can be repeated with different batches of gamma globulin and under less propitious circumstances is a question.

The allocation of gamma globulin during the 1953 poliomyelitis season presented many problems. The main question was how best to distribute the limited supply (about one million average doses) in the fairest manner so that it would do the most good. The over-dramatization and hysteria accompanying infantile paralysis served to throw gamma globulin out of perspective and multiply the administrative headaches of everybody concerned from the national level to the state health departments and practicing physicians. Had the disease been measles instead of poliomyelitis, the difficulties would have been easily handled. Infection with measles virus results in a readily recognized disease 99 times in 100. Most individuals know even years later whether or not they have had measles. In poliomyelitis the reverse is nearer the truth. Paralysis has come to be regarded as an accident of poliomyelitis, the vast majority being non-paralytic, abortive, or inapparent infections. At present there is no practical test of immunity (like the Schick test for diphtheria) available for poliomyelitis. In addition, exposure to measles is usually determined with accuracy, gamma globulin may be given to the contacts at the appropriate time, and measles is prevented or modified accordingly. In poliomyelitis, on the other hand, it is rarely possible to trace accurately the source of infection.

The importance of the family as a focus of poliomyelitis infection is well established[12,26,28]. One method of distributing gamma globulin in 1953 was to supply it to familial or household contacts. Although virus may be detected in the stools of various members of the household, and some of them may undergo a "minor" illness, it is uncommon to have more than one

paralytic case in the same family during the same epidemic. Siegel and Greenberg[25] made a thorough study of multiple cases in New York City households during the period 1949 to 1952, which included one epidemic year. Only about 4% of the affected families had more than one case. Of all cases, only 60% were paralytic. Moreover, the onset of illness in over 90% of the multiple cases took place within 12 days of onset of the index case. Allowing an average of 4 or 5 days' delay in making the diagnosis, this leaves but a small fraction in which gamma globulin might have had a chance to be effective. By limiting gamma globulin to household contacts, therefore, one would miss a large portion (as much as 96%) of individuals who acquire poliomyelitis. Essentially this method of distribution was employed in certain areas by state health departments faced with not enough material to go around.

The method of mass community prophylaxis has in its favor the successful field trial at least in the Iowa area, and the repeated observation that most cases of poliomyelitis originate from contact with unrecognized sources. It also has disadvantages. In addition to the problems of supply and administration, the question of whether or not a given community has an outbreak of sufficient proportions to warrant its use is difficult to settle. Sabin has pointed out that "there is only one rational basis for using gamma globulin and that is to administer it to those at greatest risk in areas with a very high incidence of the paralytic disease"[23]. One could make the inference that an epidemic such as the one which occurred in 1952 in Harris County, Texas, where the effect of gamma globulin was not impressive despite a morbidity rate of approximately 82 per 100,000 population, is not suitable for gamma globulin. Yet it was the severest epidemic ever experienced by this area and comparable attack rates are rarely attained in urban and semiurban groups of 600,000 to 1,000,000 people. The role of gamma globulin will indeed be small if it requires the extraordinarily high case rates of about 400 per 100,000 (Iowa) to be demonstrable.

During the summer of 1953, mass prophylaxis with gamma globulin was attempted in 23 communities. A total of approximately 226,000 persons (mostly children under 15 years) was inoculated[20]. At the present writing it is impossible to say whether or not gamma globulin prevented any poliomyelitis. This is because for the most part controlled studies were not carried out. The material was administered in service programs based on the assumption that it would do some good. In North Carolina, gamma globulin was injected after the peak of the epidemics had been reached and at a period when the "number of cases was declining sharply"[20]. In Catawba County, 14,761 children under 10 years were inoculated; 15 of them developed poliomyelitis; 13 were paralytic cases. However, all but 2 developed symptoms within one week of injection, a period during which Hammon and his co-workers observed no protection. It is doubtful that gamma globulin influenced the course of the epidemic. In New York State mass prophylaxis was carried out in 2 counties: Chemung and Steuben. All told, 37,000 children, aged 6 months to 10 years, were inoculated with gamma globulin. Korns[20] has indicated that 75% of cases reported before the giving of injections were under 10 years of age, while after gamma globulin was given, only 35% were in that age group. One might immediately draw the conclusion that since gamma globulin was given to children under 10 years of age, the shift was due directly to the

prevention of disease in this group. Korns observed, however, that similar shifts in age incidence were commonly seen in epidemics where no gamma globulin was used.

If gamma globulin is going to be used on a large scale in circumstances where its beneficial effect is doubtful, at least one would like to know whether or not its effect may be harmful. Is it possible that the administration of passive antibody may suppress active immunity naturally acquired in the course of infection? Bodian fed large amounts of virus to chimpanzees immediately after they had been passively immunized with specific hyperimmune serum[6]. Virus was detected in the feces from 2 to 4 weeks after feeding. The titers of fecal virus in the immunized animals were the same as those in the controls, indicating no suppression of fecal virus excretion by passive antibody. Although the emergence of active antibody was delayed, eventually all but 2 of the 9 treated animals showed levels comparable to the controls. Sabin[23] makes the comment that, whereas large amounts of virus have been shown capable of producing active immunity in animals despite the presence of circulating passive antibody, it is not known what small doses of virus would do under similar circumstances. Furthermore, information is lacking as to what may happen in large segments of the population under natural conditions. Brown[8] detected virus in the stools of familial associates given gamma globulin. The titers ranged from 10^{-1} to 10^{-6}. Although the results of tests for antibody rises in these individuals are not known at present, it would be logical to expect that concentrations of virus in the stools as high as 10^{-6} would be associated with an active antibody response. Preliminary results on material collected by Hammon and his associates during and after the field trials showed no interference with active antibody response in about 20 contacts who received gamma globulin[8a].

Conclusion. Gamma globulin appears to be a temporizing measure in the prevention of poliomyelitis. Granting the ability of properly constituted batches of gamma globulin to confer temporary passive immunity, its value is best demonstrated in a severe epidemic with an unusually high attack rate. Although limited observations suggest that gamma globulin does not interfere with naturally acquired active immunity, the wisdom of using it widely in the absence of an epidemic is doubtful. From a practical point of view its usefulness is seriously limited because of the nature of the disease: unknown methods of transmission, unrecognizable sources of infection and, consequently, time of exposure, and present impracticability of distinguishing immune from susceptible individuals. These features, inherent in poliomyelitis, make it necessary to administer gamma globulin to thousands in order to prevent one paralytic case.

REFERENCES

(1) **Bahlke, A. M.,** and **Perkins, J. E.:** J. Am. Med. Assn., **129,** 1146, 1945. (2) **Bell, J. A.:** Am. J. Dis. Child., **86,** 311, 1953. (3) **Bodian, D.:** Proc. Soc. Exp. Biol. & Med., **72,** 259, 1949. (4) Idem: Fed. Proceed., **12,** 436, 1953. (5) Idem: Am. J. Hyg., **56,** 78, 1952. (6) Idem: Ibid, **58,** 81, 1953. (7) **Boyd, T. E.:** Bact. Rev., **17,** 339, 1953. (8) **Brown, G. C.:** Personal communication.

(8a) **Coriell, L. L.:** Data presented at 81st Annual Meeting, American Public Health Association, New York City, Nov. 12, 1953.

(9) **Enders, J. F.:** J. Clin. Invest., **23,** 510, 1944. (10) Idem: J. Immunol., **69,** 639, 1952. (11) **Enders, J. F., Weller, T. H.,** and **Robbins, F. C.:** Science, **109,** 85, 1949.

(12) **Francis, T., Jr.**: Tr. Assn. Am. Phys., **65,** 176, 1952.
(13) **Hammon, W. McD.**: Am. J. Med. Sci., **226,** 125, 1953. (**14**) Idem: Bull. New York Acad. Med., **29,** 930, 1953. (**15**) **Hammon, W. McD., Cheever, F. S.,** and **Sather, G. E.**: Proc. Soc. Exp. Biol. & Med., **80,** 150, 1952. (**16**) **Hammon, W. McD., Coriell, L. L.,** and **Stokes, J., Jr.**: J. Am. Med. Assn., **150,** 739, 1952. (**17**) Idem: Ibid., **150,** 750, 1952. (**18**) **Hammon, W. McD., Coriell, L. L., Wehrle, P. F., Klimt, C. R.,** and **Stokes, J., Jr.**: Ibid., **150,** 757, 1952. (**19**) **Hammon, W. McD., Coriell, L. L., Wehrle, P. F.,** and **Stokes, J., Jr.**: Ibid, **151,** 1272, 1953. (**20**) Hearings before the Committee on Interstate and Foreign Commerce, House of Representatives, 83rd Congress. First Session on the Causes, Control, and Remedies of the Principal Diseases of Mankind. Part 3. October 6 and 12, 1953. (Poliomyelitis). U. S. Government Printing Office, Washington: 1953.
(21) **Melnick, J. L.,** and **Ledinko, N.**: J. Inf. Dis., **90,** 279, 1952.
(22) **Robbins, F. C., Enders, J. F.,** and **Weller, T. H.**: Proc. Soc. Exp. Biol. & Med., **75,** 370, 1950.
(23) **Sabin, A. B.**: Ohio State Med. J., **49,** 603, 1953. (**24**) **Salk, J. E.**: Pediatrics, **12,** 471, 1953. (**25**) **Siegel, M.,** and **Greenberg, M.**: New England J. Med., **249,** 171, 1953.
(26) **Wenner, H. A.,** and **Tanner, W. A.**: Am. J. Med. Sci., **216,** 258, 1948.
(27) **Youngner, J. S.**: Proc. Soc. Exp. Biol. & Med., **84,** 697, 1953.
(28) **Zintek, A. R.**: Am. J. Hyg., **46,** 248, 1947.

RADIOLOGY

UNDER THE CHARGE OF

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BIOCHEMICAL CONSIDERATION OF DISTRIBUTION

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AN adequate basis for either the diagnostic or the therapeutic use of a radiochemical is a fundamental knowledge of its distribution, localization, and excretion; that is, its total metabolic pattern in the body. Extensive empirical information of this type has been accumulated for many elements and intense effort continues in this area of investigation. A scanning of volumes of Nuclear Science Abstracts and Chemical Abstracts for 1951 and 1952 showed approximately 400 references dealing with the distribution and metabolism (in mammals) of the nuclides of 60 elements.

Many studies have given attention to fission products, which include over 200 nuclides of 33 elements[20]. Approximately 85% of these nuclides are radioactive with half-life periods ranging from a few seconds to many years. For obvious reasons the nature of the problem of fission products has emphasized studies using carrier-free nuclides. Conclusions from such studies may or may not be applicable to a medical problem.

The presentation that follows gives attention to: (1) elements of primary interest, (2) certain important considerations that influence their behavior in the body, and (3) an illustration taken from a recent study in our laboratory[46].

The elements of primary interest are considered in two groups: those present in body tissue[63] and those that have been appraised to possess therapeutic potentialities[7]. Those of the first group are presented in Table 1. The last four on the list are called "trace elements." In addition to these, various others are sometimes listed including zinc, aluminum, fluorine, silicon, lithium, bromine, arsenic, lead, molybdenum, cobalt, and vanadium. The functional or adventitious presence of many of the group of trace elements is uncertain. The use of radioactive isotopes of the elements in Table 1 is primarily of concern to metabolic studies. Two of the elements present in tissue, phosphorus and iodine, are exceptions and among the most prominent of those

*Work done under contract with the United States Atomic Energy Commission.

used medically; also, isotopes of sodium and potassium are finding an increasing use in diagnostic studies. The major contribution that has come from studies using the unstable nuclides of these elements consists largely of additional fundamental knowledge of metabolic machinery. The other group of elements of interest comprises 25 nuclides selected by Bruce on the basis of half-life and feasibility of production by thermal neutron reactions[7]. These are listed in Table 2. The half-life of the nuclides in the list ranges from 12 hours to 50 days; 21 of the 25 come within a range of 12 hours to 7 days. The activation index is the product of the nuclear cross section in *barns* and the per cent abundance of the parent isotope. A noticeable gap appears between lanthanum 140 (the last in the first column) and mercury 197 (the first in the third column). In the first column appear seven nuclides of the lanthanide series of rare earth elements: lutecium 177, holmium 166, samarium 153, ytterbium 175, ytterbium 169, praseodymium 142, and lanthanum 140. Another of this series, gadolinium 159, appears at the end of the list. Yttrium 90, chemically quite similar to the lanthanides, is near gadolinium.

Several from the selected list of potentially useful nuclides have received attention in both basic and clinical studies at the Medical Division of the Oak Ridge Institute of Nuclear Studies. Gold and gallium have been studied at length; antimony and hafnium have been studied to some extent; and indium has received a small amount of attention. The high percentage of rare

TABLE 1.—APPROXIMATE ELEMENTARY COMPOSITION OF THE ADULT HUMAN BODY (Data from many sources)

Element	*Percentage*	*Grams Per 70 Kg.*
Oxygen	65.0	45,500
Carbon	18.0	12,600
Hydrogen	10.0	7,000
Nitrogen	3.0	2,100
Calcium	1.5–2.2	1,300
Phosphorus	0.8–1.2	700
Potassium	0.35	245
Sulfur	0.25	175
Sodium	0.15	105
Chlorine	0.15	105
Magnesium	0.05	35
Iron	0.004	3
Manganese	0.0003	0.210
Copper	0.00015	0.105
Iodine	0.00004	0.028

TABLE 2.—SELECTED RADIOISOTOPES FOR MEDICAL STUDY

Radioisotope	*Activation Index*	*Radioisotope*	*Activation Index*
79 Gold 198	9500	80 Mercury 197	480
71 Lutecium 177	9360	33 Arsenic 76	420
77 Iridium 194	8000	51 Antimony 122	387
67 Holmium 166	6700	72 Hafnium 181	350
75 Rhenium 188	4662	46 Palladium 109	297
75 Rhenium 186	3858	29 Copper 64	297
62 Samarium 153	3445	78 Platinum 197	275
70 Ytterbium 175	2368	49 Indium 114	240
70 Ytterbium 169	1120	76 Osmium 191	216
59 Praseodymium 142	1100	31 Gallium 72	133
74 Tungsten 187	986	39 Yttrium 90	124
57 Lanthanum 140	840	35 Bromine 82	113
		64 Gadolinium 159	100

earth elements in this selected list of potentially useful nuclides is noteworthy. Animal studies are in progress with lutecium and with yttrium; and studies using holmium are scheduled for the immediate future.

Numerous factors influence the pattern of distribution of chemical substances in the body. The more important are selected for the present discussion. One of the most obvious is the similarity among the members of a chemical family. Certain examples are common knowledge. Early studies of astatine indicate a pattern similar to that of iodine[36]. Strontium, like calcium, deposits in or exchanges into the mineral structure of bone, in contrast to some other cations, which are associated with the organic component of the skeleton[17,33]. Conditions that affect the metabolism of one type may not influence the other[41]. A less frequently emphasized example of biological similarity among elements is that of potassium and rubidium[11] cited by Clark as early as 1921. In 1935, Lasnitzki and Szorenyi found rubidium to substitute for potassium in an enzyme system from yeast[47]. In other enzyme systems for which potassium is considered essential the substitution is claimed to apply[6,43]. Greenberg[28] found Rb and K to have a similar rate of disappearance in plasma, and growth has been reported on a potassium-deficient rubidium-supplemented diet. Extending this family characteristic to another member, the distribution of cesium appears somewhat similar to the potassium pattern but less so than rubidium[15,61]. The interchangeability of rubidium and potassium has recently been used in a study not possible with potassium because of its short half-life (K^{42}, 12.4 hrs; Rb^{86}, 19 days)[4]. The family pattern among elements influenced our program of study of lutecium and holmium, both of which are lanthanides, and of yttrium, which chemically is quite similar. Contrasting exception for the Fe, Co, and Ni group is suggested by recent work with nickel[75].

Fission products include the full range of elemental types from the inert gases to the very active halogens and alkali metals[20]. Studies of the metabolism of fission products[31,32,61] show many of the metals to have certain similarities in patterns of absorption, deposition, distribution, and excretion which overlap considerably from one family of elements to another[34,35,36]. This similarity may be related to their property of forming insoluble hydroxides at the pH of body fluids. Such insoluble hydroxides may then be handled in a way more dependent upon the physical state than on the chemical composition.

A general property common to some of the heaviest and some of the lightest of the nuclides is applicable at extremely low concentration and may profoundly affect the metabolic pattern of a wide variety of radiochemicals. This is called the radiocolloidal property of the substance. The term makes for some confusion, since colloids labeled with radioactive isotopes assume a prominent place among current studies of radioactive therapeutic agents. The phenomenon is, however, something different. Investigation of radiocolloids began apparently by accident in 1913 when Paneth[53,54] noted a difference in the dialyzability of radium D (Pb 210), E (Bi 210), and F (Po 210). Very little was added to the subject during the next 25 years when a few scattered reports appeared. Numerous reports have followed in the past 4 or 5 years[57,58]. At the present time this surprising property has been observed for approximately 20 metals ranging from $_4Be^9$ to $_{40}Th^{232}$. At concentrations several orders of magnitude

less than the solubility, according to the usually accepted solubility product, the element behaves like a colloid. This property had to await carrier-free radioactive nuclides to provide a sufficiently sensitive means of study. The colloidal properties of these systems have been observed from several approaches, including removal by filtration or centrifugation, non-dialyzability, diffusion coefficients, electrophoretic mobilities, response to ion exchange columns, autoradiography, and other methods. Figure 1 represents the effect of concentration on the tendency of certain elements to yield radiocolloids. This tendency has been observed to be dependent on concentration for various elements[10,30,44,45]. The position of the curve on the abscissa will vary from one element to another, since the ascending limb at the right reflects solubility. Figure 2 shows the effect of pH on the radiocolloidal property of lanthanum[59]. The shape of the curve is strikingly similar to a titration curve of weak acid or an easily hydrolyzed salt of a weak base and strong acid. The curve is displaced on the abscissa, however, from the position of the titration curve of lanthanum chloride. Figure 3 is a similar treatment of yttrium 90[60]. Four curves which are in general similar in shape but slightly displaced are shown. The curves show the effect of different salts, different concentrations of the same salt, and the effect of complexing $Y(OH)_3$ with carbonate. The application of radiocolloidal effects to studies *in vivo* appears self-evident.

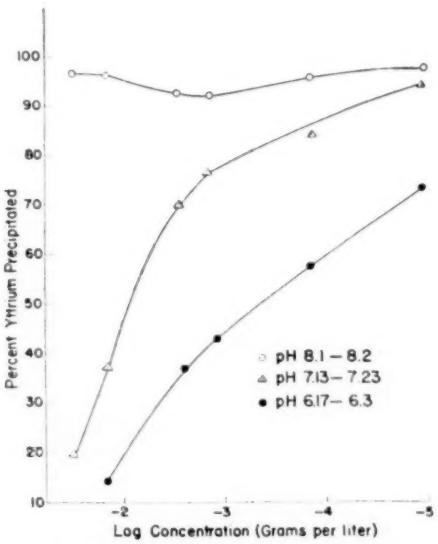
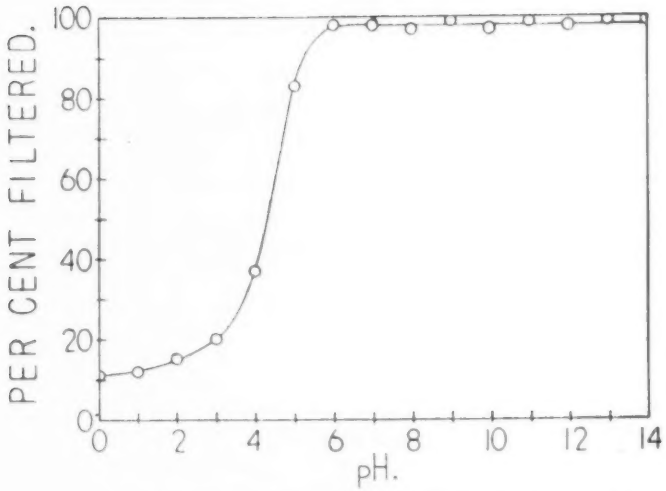
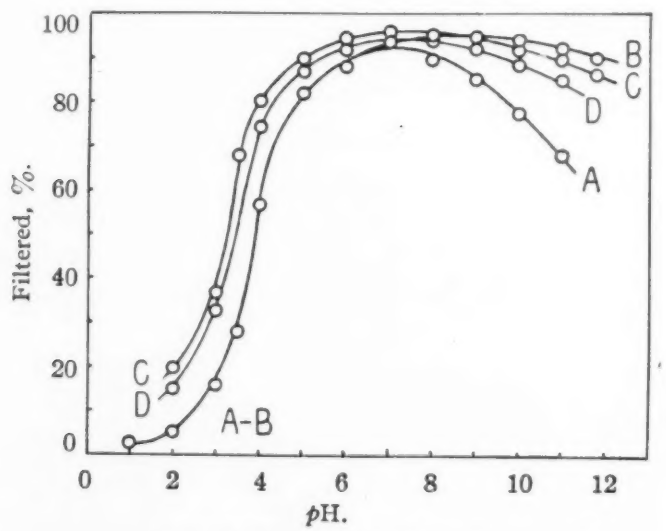


Fig. 1.—The three curves show that the percentage of ionic yttrium that exists in an aggregated state depends both on concentration and on pH. The precipitated fraction plotted on the ordinate is the amount that is observed experimentally to be filtrable or centrifugable. The extremes of the units plotted on the abscissa are equivalent to a range from 1.1×10^{-3} to 1.1×10^{-7} moles per liter. Although the percentage in the aggregated state increases sharply at the same pH as concentration decreases, the absolute amount decreases. Above pH 8.1, the effect of concentration is small. (Kurbatov and Kurbatov, Courtesy of J. Phys. Chem.)



Per cent. lanthanum-140 filtered *vs.* *p*H obtained by neutralizing a solution 1.0 *N* in nitric acid with carbonate-free sodium hydroxide solution.

Fig. 2.—The measurements were made with approximately 10^{-12} molar solutions of lanthanum prepared free of carrier from a mixture of barium 140 and lanthanum 140. In similar series, the concentration of nitric acid and the base used in the titration were varied to compare the effect of other salts and their concentration. The filtrable aggregate is reduced by increasing the concentration of salt. The effect is more prominent with citrate, carbonate, or oxalate, than with nitrate. (Schweitzer, Stein and Jackson, Courtesy of J. Am. Chem. Soc.)



Percentage yttrium-90 filtered *versus* *p*H.

Fig. 3.—The radioactive yttrium was prepared free of carrier from a mixture of strontium 90 and yttrium 90. The concentration was approximately 10^{-11} molar. The four curves represent different conditions as follows: A, 0.1 M hydrochloric acid titrated with 0.1 M sodium hydroxide contaminated by carbonate from the air; B, similar to A but without contamination by carbonate; C and D, 0.01 M hydrochloric acid titrated with sodium hydroxide and ammonium hydroxide, respectively, in the absence of carbonate. (Schweitzer, Stein and Jackson, Courtesy J. Am. Chem. Soc.)

The pH of body fluids is favorable to the formation of radiocolloids when carrier-free or very high specific activity material is in use. There is an urgent need for studies of these properties in tissue fluids and plasma in order to be able to extrapolate with some degree of correctness from *in vitro* to *in vivo* environments.

ministered colloids has been broad. A wide variety of colloids has been studied including: calcium phosphate[25,26], ferric hydroxide[5], manganese[19,62], the macromolecules of certain dyes and proteins[16,73], the lanthanide[18] and actinide elements[24,27,55], chromic phosphate[1,42,52], gold[2,29], and many other substances. The charge, size, and

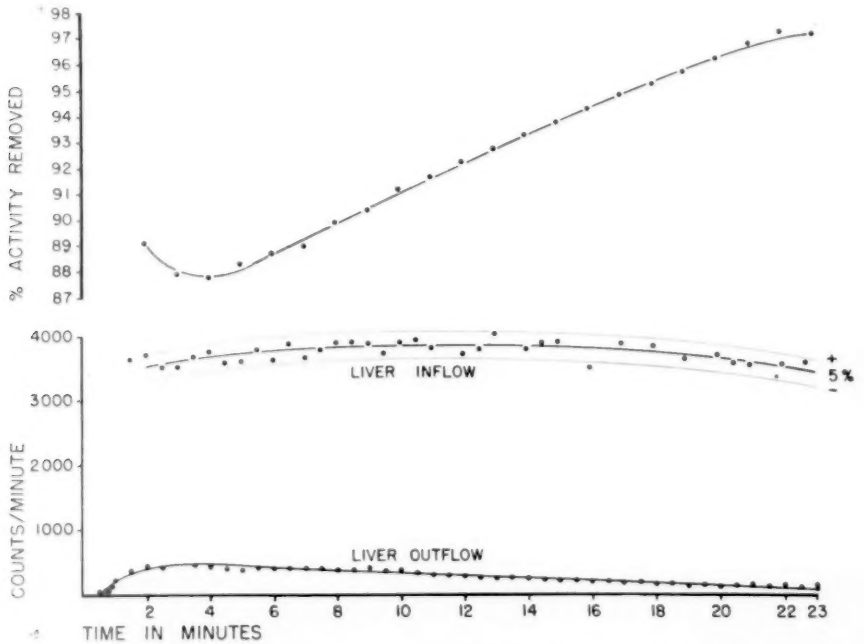


Fig. 4.—The concentration of radioactive colloidal gold flowing into the liver is shown by the second curve. The lowest curve is a plot of the activity remaining in the blood after passing through the liver. The colloid that was removed is expressed as per cent of the total presented to the liver and is plotted in the uppermost curve. The efficiency with which the colloid is removed is high from the beginning and increases in a regular manner after four minutes. (Little and Kelly, Courtesy Am. J. Physiol.)

Brief attention is called to the effects of different preparations of a radioactive substance on its distribution. These are considered with respect to physical differences and chemical characteristics. The physical characteristics to be discussed are based on considerations of colloidal systems. The study of the response of a mammalian organism to intravenously and intracavitarily administered colloids has been broad. A wide variety of colloids has been studied including: calcium phosphate[25,26], ferric hydroxide[5], manganese[19,62], the macromolecules of certain dyes and proteins[16,73], the lanthanide[18] and actinide elements[24,27,55], chromic phosphate[1,42,52], gold[2,29], and many other substances. The charge, size, and chemical nature are prominent factors that influence the distribution of a colloidal preparation. Gabrielli describes, in a series of publications, the use of chromic phosphate to "titrate" the functional capacity of the reticuloendothelial system by measuring uptake in the liver[21,22,23]. The studies of Dobson, Gofman, *et al.* suggest some degree of controlled localization on the basis of

particle size and chemical nature[18]. Zilversmit, Boyd, and Brucer[77] have recently presented a method whereby monodisperse radioactive gold sols can be prepared and their particle size measured by low-speed centrifuging. The method is sufficiently simple for routine use in characterizing radioactive sols before administration. Little and Kelly recently reported an important finding from work done in our laboratories during the summer of 1952[48]. They measured the uptake of radioactive colloidal gold during a single

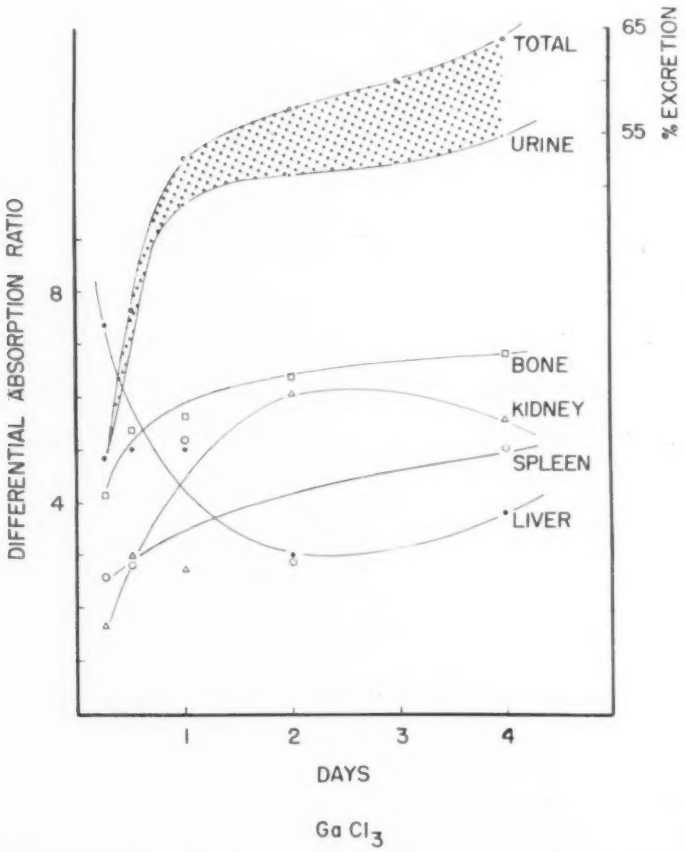


Fig. 5.—The distribution of gallium chloride labeled with gallium 72 after intravenous administration to rats. The radioisotopic label, Ga 72, was produced by the reaction of stable gallium with thermal neutrons. The isotope decays with a half life of 14.3 hours emitting a variety of beta and gamma rays ranging in energy from 3.15 to 0.64 and from 2.51 to 0.63 million electron volts, respectively. The specific activity was 0.2 millicuries or less per milligram. The gallium chloride was prepared at pH 2.0 to 2.2 by an excess of hydrochloric acid in order to prevent insolubility which results by hydrolysis of the salt. Each point in the figure is the average result from 5 rats studied separately. The *differential absorption ratio*, the DAR of Marinelli, appearing on the ordinate is defined by

$$\frac{\text{Activity/gram of tissue}}{\text{Total retained activity / body weight}}$$

(Brucer, M., *et al.*, Courtesy Radiology)

passage of blood through "normal" bile-producing dog liver for which separate circulation was established. Figure 4 summarizes their observations. Fractional samples were taken at 30-second intervals; the rate of flow and the ra-

response of the body to a colloidal preparation.

A very important chemical consideration of radiochemical preparations involves the use of complexing agents. Their use may profoundly change the

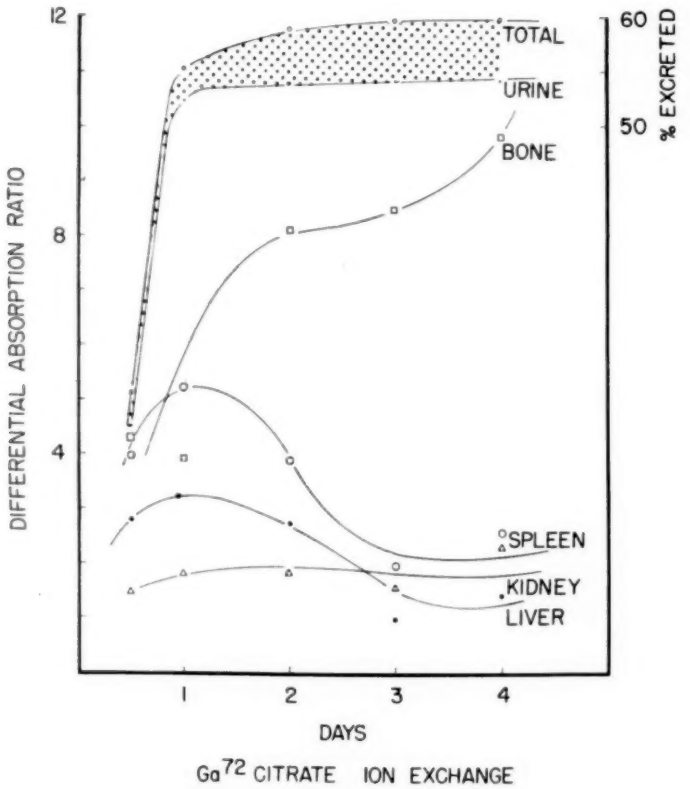


Fig. 6.—The distribution of gallium citrate labeled with gallium 72 following intravenous administration to rats. The citrate is a stable soluble complex that was adjusted to pH 7.4 and administered concurrently with 2 moles of calcium per mole of citrate. Other specifications of the radioisotope and definition of units that pertain to the figure are the same as for Fig. 5. Each point is the average of 4 rats studied separately. (Brucer, M., *et al.*, Courtesy Radiology)

dioactivity were measured; the percentage of the total activity presented to the liver was calculated and presented in the curve at the top of the figure. These selected studies illustrate useful approaches for the interpretation of the

pattern of distribution of many elements. The common complexing agents include both inorganic and organic substances. These are in many instances illustrated by old and well established procedures of inorganic and analytical

chemistry. The complexing agent serves to bind the ion firmly in a form in which it does not respond to its usual reactions[40]. Soluble complexes formed by the interaction of certain organic structures and cations, which as uncomplexed ions are insoluble at the pH of the body, are receiving increased emphasis in studies of the metabolic pattern of many inorganic substances. It should be noted that certain complexing agents can be metabolized and, in fact, constitute a unit in the metabolic pool. Citrate and other hydroxy acids, polyhydric alcohols such as the simple sugars, and amino acids are examples. Others are substances that are quite resistant to metabolism and depend upon excretory channels for their removal from the body. The degree of dissociation of a complex into its constituent parts and the response of the

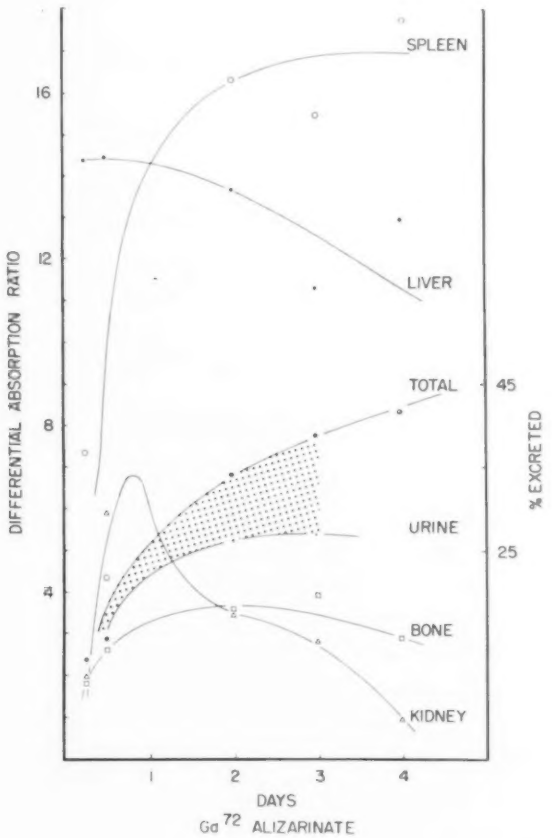
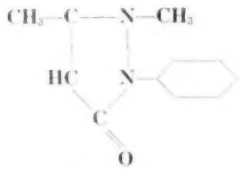


Fig. 7.—The distribution of gallium alizarinate labeled with gallium 72 following intravenous administration to rats. The alizarinate of gallium is an insoluble but highly dispersed chelate. The preparation was conveniently accomplished in dilute sodium bicarbonate and adjusted to pH 7.4. Other specifications of the radioisotope and definition of units that pertain to the figure are the same as for Fig. 5. The points at 0.5, 1, and 4 days are the average of 6 separately studied rats; the remaining points are the average of 4. (Brucer, M., *et al.*, Courtesy Radiology)

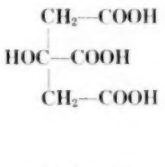
body to these parts are fundamental factors in the effect of different complexing agents on the distribution pattern of a foreign ionic species. Figures 5, 6, and 7 provide a comparison of the effect of different complexing agents on the distribution of gallium in the rat. Radioisotopes of this element have been studied rather extensively at the Medical Division for their possible

Certain complexing agents that have received prominent attention in the study of radiochemicals are illustrated by the formula below:

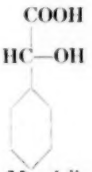
Leading all other complexing or chelating agents in the attention it has received is ethylenediaminetetraacetic acid (EDTA). Numerous articles have appeared that deal with its effect on the deposition of a metallic



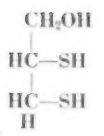
Antipyrine
(1, 5-Dimethyl-2-phenyl-3-pyrazalone.)



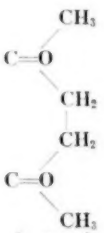
Citric acid



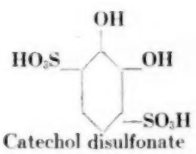
Mandelic acid



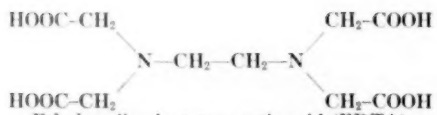
British anti Lewisite (BAL)



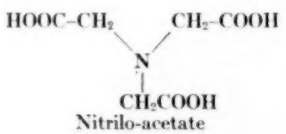
Acetonyl acetone



Catechol disulfonate



Ethylenediaminetetra-acetic acid (EDTA)
(Versene: Bersworth Chemical Co.)
(Sequestrene: Alrose Chemical Co.)



Nitrilo-acetate

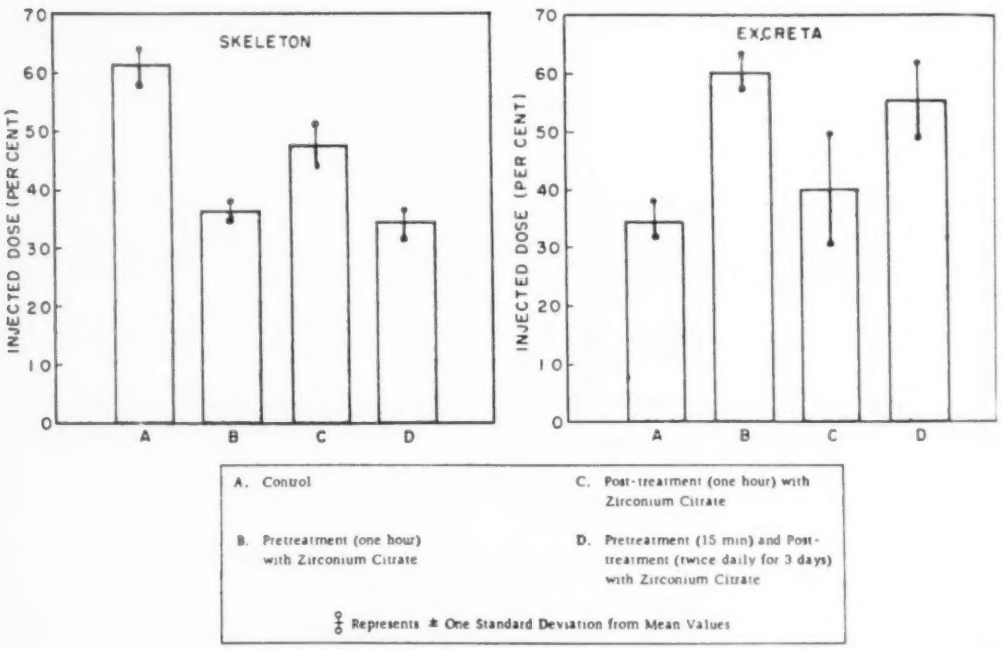
therapeutic application[8]. There is insufficient information to permit intelligent interpretation of why the differences, which appear in these figures, exist. The important fact for the moment is that a difference does exist. Differences were observed also for hafnium when administered as the chloride, the mandelate, the citrate, and catechol disulfonate[49].

ion in the body or the decontamination of a body already containing an element[3,13,14,37,38,39,51,56]. This material has been acclaimed to be the most avid of the known chelating agents. It is relatively inert metabolically, and is low in toxicity. Studies on the agent itself using C-14 labeled versene show its excretion to be practically complete in the urine in 24 hours[39]. Only a few

of the metals studied in conjunction with EDTA, fail to show a striking effect of the complexing agent. Strontium is an exception and has received much attention because of its occurrence among fission products. Figures 8 and 9 are taken from a recent report on strontium by Cohn and Gong[12].

trivalent ions such as the rare earths. Figures 10 and 11 summarize the pertinent information on these new agents.

The very practical application that may derive from studies with complexing agents relates to the possibility of decontaminating an individual after a therapeutic dose of an isotope has been



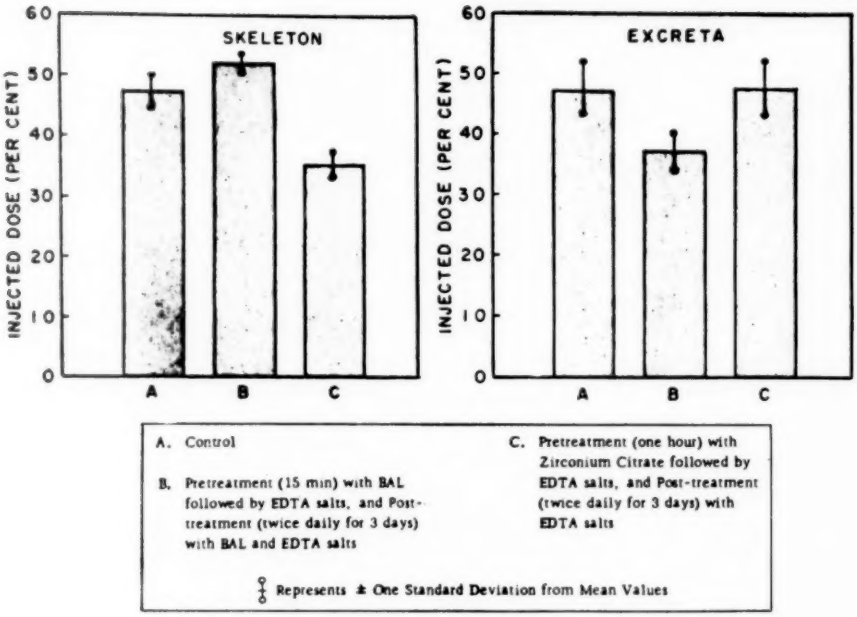
Effect of zirconium citrate on skeletal content and excretion of injected radiostrontium.

Fig. 8.—Columns A, B, C, and D represent the average of data from groups of 10, 5, 9, and 8, respectively, of individually studied animals. Sprague-Dawley rats, 3 months of age, were used. Each received 15 microcuries of strontium 89 five days before sacrifice. All injections were made intraperitoneally. (Cohn and Gong, Courtesy of Proc. Soc. Exper. Biol. & Med.)

In September, 1953, Chaberek and Bersworth announced two additional chelating agents similar to EDTA[9]. These agents exhibit a stronger avidity for iron than EDTA, even to the extent that hot strongly alkaline solutions containing ferric iron show no tendency ror the flocculation of $Fe(OH)_3$. It will be of much interest to examine the complexes of these agents with other

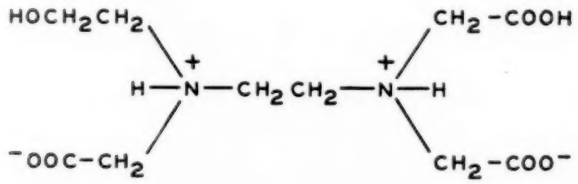
given for the desired length of time. If practical procedures for decontamination can be accomplished, the way is open for other potentially useful substances, which by present standards have too long a half-life to permit their therapeutic use.

Aside from synthetic complexing agents, the affinity of the proteins for various ions is to be kept in mind.


SKELETON
EXCRETA
INJECTED DOSE (PER CENT)
60
50
40
30
20
10
0
A
B
C
A. Control
B. Pretreatment (15 min) with BAL followed by EDTA salts, and Post-treatment (twice daily for 3 days) with BAL and EDTA salts
C. Pretreatment (one hour) with Zirconium Citrate followed by EDTA salts, and Post-treatment (twice daily for 3 days) with EDTA salts
Represents ± One Standard Deviation from Mean Values

Effect of various chemical agents on skeletal content and excretion of injected radiostrontium.

Fig. 9.—Columns A, B, and C represent averages from groups of 14, 7 and 14, respectively, of Sprague-Dawley rats 5 months of age. Each received 15 microcuries of strontium 89 five days before sacrifice and other agents at various intervals defined in the figure. All injections were intraperitoneal except BAL which was given intramuscularly in a solution of peanut oil. Salts of EDTA refers to NaEDTA and CaEDTA, 1 part and 5 parts, respectively. (Cohn and Gong. Courtesy of Proc. Soc. Exper. Biol. & Med.)



N-HYDROXYETHYLETHYLENEDIAAMINETRIACETIC ACID

$H_3A(OH) \rightleftharpoons H_2A(OH)^- + H^+$ $\quad pK_1 = 2.6$

$H_2A(OH)^- \rightleftharpoons HA(OH)^{-2} + H^+$ $\quad pK_2 = 5.1$

$HA(OH)^{-2} \rightleftharpoons A(OH)^{-3} + H^+$ $\quad pK_3 = 8.3$

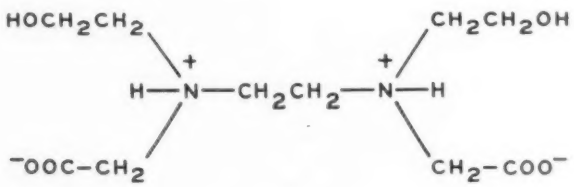
$Fe^{+3} + A(OH)^{-3} \rightleftharpoons FeA(OH)$ $\quad \log K_1 = 21$

$FeA(OH) \rightleftharpoons FeAO^- + H^+$ $\quad pK_2 = 3.8$

Fig. 10.—The name Versen-01 is assigned to this new chelating agent. The formula shows the close structural relation to EDTA (Versene, Sequestrene, etc.). One of the carboxyl groups of EDTA is replaced by a primary alcohol group. The constant for the last equation in the figure indicates that the alcohol group in the complex with iron exhibits a stronger acidic property than either the secondary or tertiary carboxylic acid of the uncomplexed Versen-01. At pH 6 the iron would exist practically 100% in stable anionic combination. (Adapted from Chaberek and Bersworth[9])

Steinhardt, *et al.* have reported a detailed study of the interaction of both soluble and insoluble proteins with a considerable number of anions and cations[64-71]. The differences among the affinities of various ions are considerable, resulting in a range of as much as 3 pH units in the position of the titration curve of the protein in the presence of certain ions.

lated to the level of interest to the therapist or toxicologist. Stokinger offers explanations based on physicochemical theory for the differences that result from varying the size of the chemical dose of radioisotopes. The pronounced influence of the size of the chemical dose should not be expected to apply to a substance for which there is a relatively large and readily ex-



N,N′—DIHYDROXYETHYLETHYLENEDIAMINEDIACETIC ACID

$$H_2A(OH)_2 \rightleftharpoons HA(OH)_2^- + H^+ \qquad pK_1 = 4.7$$

$$HA(OH)_2^- \rightleftharpoons A(OH)_2^{-2} + H^+ \qquad pK_2 = 8.6$$

$$Fe^{+3} + A(OH)_2^{-2} \rightleftharpoons FeA(OH)_2^+ \qquad \log K_1 = 15$$

$$FeA(OH)_2^+ \rightleftharpoons FeAO(OH) + H^+ \qquad pK_2 = 2.2$$

$$FeAO(OH) \rightleftharpoons FeAO_2^- + H^+ \qquad pK_3 = 5.5$$

Fig. 11.—The formula in this figure presents a derivative of Versene known as Versene-di01 in which two carboxyl groups of the tetraacetic acid are replaced by hydroxymethyl groups. Similar to Versen-01, the formation of the iron-chelate derivative enhances strikingly the acidic property of the alcoholic groups. The constants for the fourth and fifth equations indicate that below pH 2.2, a cationic chelate predominates; from pH 2.2 to pH 5.5, an isoelectric chelate; and above pH 5.5, an anionic chelate. (Adapted from Chaberek and Bersworth[9])

One of the most influential factors in the distribution of radioisotopes, and one that has not been recognized in many studies, is the effect of chemical concentration, that is, carrier-free as compared with varying amounts of carrier. A discussion of this factor by Stokinger appeared recently[72]. It should be emphasized that tracer studies using carrier-free or high activity preparations cannot be extrapolated to the exchangeable body pool. Figures 12 and 13 provide examples of two elements for which no significant body pool exists[8,74].

The influence of the route of administration on distribution is primarily a matter of the body barriers which a particular route presents. Further consideration is beyond the scope of the present discussion.

No generalizations can be made re-

garding the effect of pathology, chronic or acute, on distribution. The importance of such studies under controlled conditions relates to a better understanding of abnormal relationships by comparison with the normal. Reference to a few studies will serve to illustrate. Wish, Furth, *et al.*[76], using homologous plasma, heterologous plasma, and Evans blue in rabbits and Friedell[50], using radioactively tagged serum albumin and red cells, have shown no effect on rate of disappearance or circulatory rate due to Roentgen-irradiation. The work of Cope and Moore[16] shows the clear-cut effect of acute pathologic conditions (burns) on the passage of macromolecules across the plasma-lymph barrier. The rate of transfer of ionic bromide and bromine substituted macromolecules of dye was distinctly different in the normal animal and similar in the burned subject.

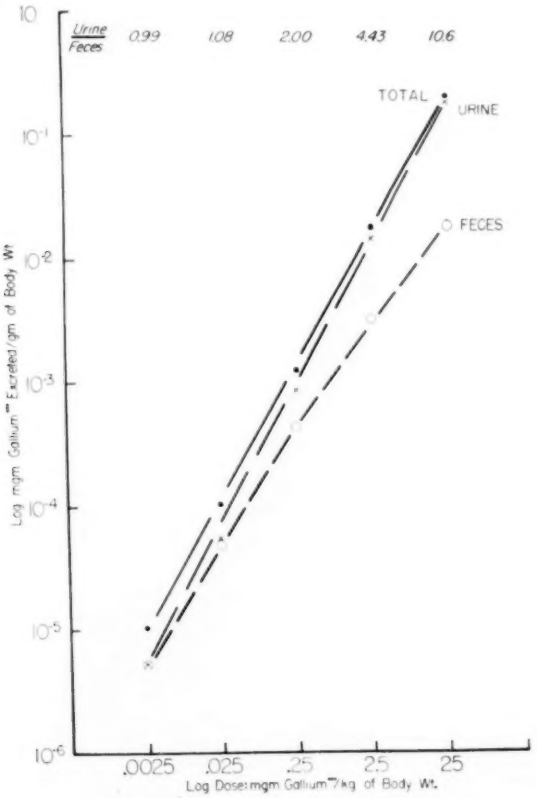


Fig. 12.—The excretion of gallium by rats during 5 days following intravenous administration of increasing doses of gallium citrate traced with radioactive gallium 67. The total, urinary, and fecal excretion are plotted on the ordinate as a logarithmic function of the total dose. The ratio of the urinary to fecal excretion is shown at the top of the figure arranged to correspond with the increasing dose. Each point is the average of 4 rats. (Brucer, M., *et al.*, Courtesy of Radiology)

Some of the previously discussed factors influencing distribution are illustrated by certain studies of yttrium cur-

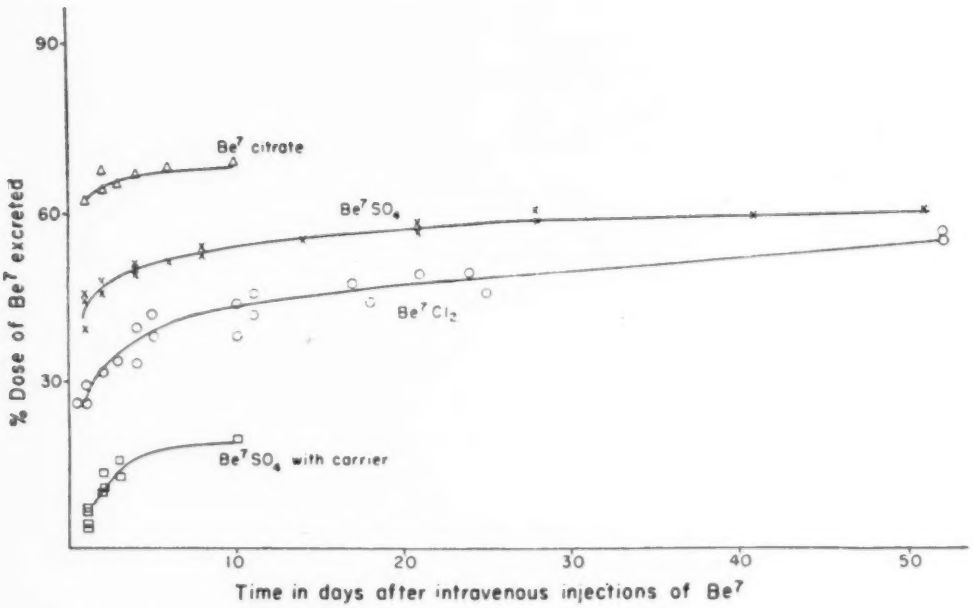


Fig. 13—The excretion of beryllium by rats following intravenous administration of beryllium 7. A comparison of the citrate, sulfate, and chloride demonstrates a distinct difference between these salts. The difference is more prominent when the sulfate with and without carrier are compared. Carrier was given at a level of 0.5 mg. per kilogram. (Van Cleave and Kaylor, Courtesy of Arch. Indus. Hyg. Occup. Med.)

TABLE 3.—DISTRIBUTION OF YTTRIUM IN THE RAT FOLLOWING INTRAPLEURAL ADMINISTRATION

(Yttrium chloride: 0.005 M, unbuffered, 1.0 cc. dose, pH 4, Y^{90} tracer)

	Per Cent of Dose			
Specimen	*18 hrs.*	*67 hrs.*	*138 hrs.*	*186 hrs.*
Heart	.614	.382	.654	.140
Left lung	5.155	6.902	7.940	9.730
Right lung	11.082	12.056	28.703	17.723
Mediastinum	32.052	37.188	32.316	31.952
External thorax	41.318	33.372	25.848	34.389
Chest wash	6.708	7.301	0.988	1.165
Total in chest	96.927	97.199	96.347	95.097
Liver	1.470	1.047	.958	1.563
Spleen	.014	.017	.028	.088
Kidneys	.009	.013	.021	.028
Femurs	.020	.049	.114	.147
Blood	.003	.002	.002	.003
Residual carcass	1.390	1.333	1.145	1.365
Total outside chest	2.906	2.460	2.266	3.192
Urine	.053	.132	.387	.412
Feces	.114	.209	1.001	1.300
Total excreted	.167	.341	1.388	1.712

rently in progress in our laboratories. Yttrium 90 as the chloride in an unbuffered solution and containing a considerable quantity of carrier was administered to rats and dogs. The results illustrate the effect of the nature of the preparation, the effect of carrier, and the effect of the route of administration. The rationale on which the preparation was based is that, with sufficient carrier and unbuffered, the yttrium should be converted almost instantly to an immobile form by buffered tissue fluids. If the reasoning is valid, the ionic preparation of yttrium should be expected to remain where placed. A similar approach should apply also to a number of other elements that may offer therapeutic potentialities. The data presented in Tables 3 and 4 support the validity of the assumption[46].

TABLE 4.—DISTRIBUTION OF YTTRIUM ADMINISTERED BY VARIOUS ROUTES TO THE RAT

	Per Cent of Dose			
Route of Administration	*1 day*	*3 days*	*6 days*	*8 days*
Intrapleural (Cav.; 96.39)*	96.93	97.20	96.35	95.10
(Excreted)	.17	.34	1.39	1.71
Intramuscular (Muscle; 96.08)*	98.12	95.76	94.36	
(Excreted)	.86	3.22	4.66	
Intraperitoneal (Cav.; 95.37)*	98.12	93.67	94.30	
(Excreted)	.15	.53	1.33	
Subcutaneous (Skin; 98.29)*	98.51	97.23	99.12	
(Excreted)	.76	2.24	.69	

* Average for all animals of amount remaining in site of injection.

The pattern of distribution following intrapleural administration is shown in detail in Table 3. Practically all the dose remains in the cavity throughout the longest observed period which approximates three half-lives of yttrium 90. As shown by the small fraction of the dose found in the washings and the distribution within the chest, the dose is fixed rapidly to the various pleural surfaces. The liver accounts for almost half of the unexcreted extrapleural fraction. The fraction of the dose found in the femurs and in the excreta increase slightly with time. Fecal excretion exceeds renal excretion. A comparison of the results from different routes of administration is summarized in Table 4. The preparations in each route were similar. The table records only two fractions of each dose: (1) the total remaining at the site of injection and (2) the total excreted. The average of the first, for all animals of a series, is shown parenthetically in the first column. The sum of the first and second approaches 100%. Therefore, a very small fraction of the dose is distributed elsewhere in the body. For each route of administration, the pattern of excretion is quite similar to that shown in Table 3. Slightly more of the intraperitoneal dose left the site of administration than by either of the other routes.

Summary. There are several well established factors known to influence prominently the metabolic pattern of distribution of internally administered radioisotopes. The potential value of most isotopes for internal use in therapy remains largely obscure. New ones will undoubtedly arouse interest and offer apparent advantages. Besides the

many factors profoundly affecting their distribution, removal of internally administered radioisotopes is in general an unsolved problem. Extensive information and experience from the study of a radioisotope in animals prior to its medical use are therefore emphasized as measures of extreme importance.

REFERENCES

(1) **Allen, H., Hempelmann, L. H., Jr.,** and **Womack, N. A.**: Cancer Res., **5**, 239, 1945. (2) **Andrews, G. A., Root, S. W.,** and **Kniseley, R. M.**: Cancer, **6**, 294, 1953.

(3) **Bellin, J.,** and **Laszlo, D.**: Science, **117**, 331, 1953. (4) **Berkut, M. K.**: Doctoral Dissertation, Univ. of North Carolina, June, 1953. (5) **Blau, M., Sinason, H.,** and **Baudisch, O.**: Science, **103**, 744, 1946. (6) **Brown, G. L.,** and **Feldberg, W.**: J. Physiol., **86**, 290, 1936. (7) **Brucer, M.**: Merck Report, **61**, 9, 1952. (8) **Brucer, M., Andrews, G. A.,** and **Bruner, H. D.**: Radiology, **61**, 534, 1953.

(9) **Chaberek, S., Jr.,** and **Bersworth, F. C.**: Science, **118**, 280, 1953. (10) **Chamie, C.,** and **Haissinsky, M.**: Compt. rend., Acad. Sc., Paris, **198**, 1229, 1934. (11) **Clark, A. J.**: J. Pharmacol. & Exp. Therap., **18**, 423, 1921. (12) **Cohn, S. H.,** and **Gong, J. K.**: Proc. Soc. Exp. Biol. & Med., **83**, 550, 1953. (13) Iidem: USNRDL–393, 1953. (14) **Cohn, S. H., Gong, J. K.,** and **Fishler, M. C.**: Nucleonics, **11**, No. 1, 56, 1953. (15) **Comar, C. L.**: ORO–77, 1952. (16) **Cope, O.,** and **Moore, F. D.**: J. Clin. Invest., **23**, 241, 1944. (17) **Copp, D. H., Axelrod, D. J.,** and **Hamilton, J. G.**: Am. J. Roentgenol. & Radium Therapy, **58**, 10, 1947.

(18) **Dobson, E. L., Gofman, J. W., Jones, H. B., Kelly, L. S.,** and **Walker, L. A.**: J. Lab. & Clin. Med., **34**, 305, 1949. (19) **Drinker, C. K.,** and **Shaw, L. A.**: J. Exp. Med., **33**, 77, 1921.

(20) **Friedlander, G.,** and **Perlman, M.**: Chart of the Nuclides, Knolls Atomic Power Laboratory, General Electric Co., 4th ed., 1952.

(21) **Gabrielli, E. R.**: Nature, **168**, 467, 1951. (22) Idem: Acta path. microbiol. scand., **31**, 195, 1952. (23) Idem: Fed. Proc., **12**, 47, 1953. (24) **Gaunt, W. E.,** and **Wright, G. P.**: J. Infec. Dis., **67**, 217, 1940. (25) **Gersh, I.**: Am. J. Physiol., **121**, 589, 1938. (26) Idem: Anat. Record, **70**, 331, 1938. (27) **Gordon, A. S.,** and **Katsh, G. F.**: Ann. New York Acad. Sci., **52**, 1, 1949. (28) **Greenberg, D. M., Aird, R. B., Boelter, M. D. D., Campbell, W. W., Cohn, W. E.,** and **Murayama, M. M.**: Am. J. Physiol., **140**, 47, 1943.

(29) **Hahn, P. F., Goodell, I. P. B., Sheppard, C. W., Cannon, R. O.,** and **Francis, H. C.**: J. Lab. & Clin. Med., **32**, 1442, 1947. (30) **Haissinsky, M.**: Compt. rend. Acad. Sc., Paris, **198**, 580, 1934. (31) **Hamilton, J. G.**: MDDC–1000. (32) Idem: MDDC–1062. (33) Idem: Radiology, **49**, 325, 1947. (34) Idem: AECD–2012, 1948. (35) Idem: AECD–2928, 1950. (36) Idem: UCRL–683, AECD–2901; UCRL–960, AECD–3141; UCRL–1143, AECD–3200, 1950. (37) **Hamilton, J. G.,** and **Scott, K. G.**: UCRL–1905, 1952. (38) Iidem: Proc. Soc. Exp. Biol. & Med., **83**, 301, 1953. (39) **Hart, H.,** and **Laszlo, D.**: Science, **118**, 24, 1953.

(40) **Johnson, I. R.**: Gilman, Organic Chemistry. New York, John Wiley and Sons, 2nd ed., Ch. 25, 1821, 1943. (41) **Jones, D. C.,** and **Copp, D. H.**: J. Biol. Chem., **189**, 509, 1951. (42) **Jones, H. B., Wrobel, C. J.,** and **Lyons, W. R.**: J. Clin. Invest., **23**, 783, 1944.

(43) **Kachmar, J. F.,** and **Boyer, P. D.**: Fed. Proc., **10**, 204, 1951. (44) **Kurbatov, J. D.,** and **Kurbatov, M. H.**: J. Phys. Chem., **46**, 441, 1942. (45) **Kurbatov, M. H.,** and **Kurbatov, J. D.**: J. Chem. Phys., **13**, 208, 1945. (46) **Kyker, G. C., Gleason, G. I.,** and **Cress, E. A.**: Unpublished.

(47) **Lasnitzki, A.,** and **Szorenyi, E.**: Biochem. J., **29**, 580, 1935. (48) **Little, R. C.,** and **Kelly, H. B.**: Am. J. Physiol., **173**, 265, 1953.

(49) **Macdonald, E.,** and **Bahner, C. T.**: Proc. Soc. Exp. Biol. & Med., **83**, 801, 1953. (50) **MacIntyre, W. J., Friedell, H. L.,** and **Berg, M.**: Western Reserve University Report No. 110; NYO–4014. (51) **Mitchell, W. G.**: Proc. Soc. Exp. Biol. & Med., **83**, 346, 1953. (52) **Morton, M. E.**: Nucleonics, **10**, No. 11, 92, 1952.

(53) **Paneth, F.**: Kolloid Ztschr., **13**, 297, 1913. (54) Idem: Monatsh. f. Chemie u. verwandte Teile anderer Wissenshaften, **34**, 401, 1913.

(55) **Reeves, R. J.**, and **Morgan, I. E.**: Radiology, **29**, 612, 1937. (**56**) **Rubin, M., Gignac, S., Bessman, S. P.**, and **Belknap, E. L.**: Science, **117**, 659, 1953.
(57) **Schubert, J.**, and **Conn, E. E.**: Nucleonics, **4**, No. 6, 2, 1949. (**58**) **Schweitzer, G. K.**, and **Jackson, M.**: J. Chem. Educ., **29**, 513, 1952. (**59**) **Schweitzer, G. K.**, and **Jackson, W. M.**: J. Am. Chem. Soc., **74**, 4178, 1952. (**60**) **Schweitzer, G. K., Stein, B. R.**, and **Jackson, W. M.**: J. Am. Chem. Soc., **75**, 793, 1953. (**61**) **Scott, K. G., Overstreet, R., Jacobson, L., Hamilton, J. S., Fisher, H., Crowley J., Chaikoff, I. L., Entenman, C., Fishler, M., Barber, A. I.**, and **Loomis, F.**: MDDC–1275, Chap. 13. (**62**) **Sheppard, C. W., Wells, E. B., Hahn, P. F.**, and **Goodell, J. P. B.**: J. Lab. & Clin. Med., 32, 274, 1947. (**63**) **Sherman, H. C.**: Chemistry of Food and Nutrition. New York, The Macmillan Co., 7th edition, p. 226, 1946. (**64**) **Steinhardt, J.**: J. Res. Natl. Bur. Stand., **28**, 191, 1942. (**65**) Idem: Ibid., **29**, 425, 1942. (**66**) **Steinhardt, J.**, and **Fugitt, C. H.**: Ibid., **29**, 315, 1942. (**67**) **Steinhardt, J., Fugitt, C. H.**, and **Harris, M.**: Ibid., **25**, 519, 1940. (**68**) Iidem: Ibid., **26**, 293, 1941. (**69**) Iidem: Ibid., **28**, 201, 1942. (**70**) Iidem: Ibid., **29**, 417, 1942. (**71**) Iidem: Ibid., **30**, 123, 1943. (**72**) **Stockinger, H. E.**: Nucleonics, **11**, No. 4, 24, 1953.
(73) **Tobin, L. H.**, and **Aub, J. C.**: J. Clin. Invest., **22**, 161, 1943.
(74) **Van Cleave, C. D.**, and **Kaylor, C. T.**: Arch. Indust. Med. Occup. Med., **7**, 367, 1953.
(75) **Wase, A. W., Goss, D. M.**, and **Boyd, M. J.**: Abstracts, Div. Biol. Chem., Am. Chem. Soc. p. 64C, Sept. 6-11, 1953. (**76**) **Wish, L., Furth, J., Sheppard, C. W.**, and **Storey, R. H.**: Am. J. Roentgenol. & Rad. Therap., **67**, 628, 1952.
(77) **Zilversmit, D. B., Boyd, G. A.**, and **Brucer, M.**: J. Lab. & Clin. Med., **40**, 261, 1952.

Erratum: In the April issue, the plates of Fig. 1, on page 429, and Fig. 2, on page 430, should be transposed. The legends are correct as printed.

PHYSIOLOGY

PROCEEDINGS OF

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Alveolar Ventilation at Very Low Tidal Volumes. W. A. Briscoe, M.D., R. E. Forster, M.D., and J. H. Comroe, Jr., M.D. (Departments of Physiology, Pharmacology and Anesthesiology, Graduate School of Medicine, University of Pennsylvania). It is customary to compute the volume of a given inspiration which reaches the alveoli by subtracting the respiratory dead space from the tidal volume. However, Henderson (Am. J. Physiol., **38**, 1, 1915) suggested that a "spike" of inspired gas reaches the alveoli before a volume equal to the dead space has been inspired. Furthermore, one of us studied a patient whose tidal volume was only two-thirds of his estimated dead space, and yet his arterial blood was saturated while he breathed 100% oxygen. We investigated this problem by having a normal seated subject inspire small volumes (30 cc. or greater) of 80% He —20% O_2 from a 1-liter recording spirometer and then expire maximally, while we continuously recorded the He concentration at his lips with a mass spectrometer. From the average expired alveolar He concentration and independent knowledge of the alveolar volume, we calculated the volume of inspired gas that entered the alveoli. In 5 normal subjects, He appeared in the expired alveolar gas after an inspiration of as little as 50 cc. (dead space approximately 170 cc.). The volume of inspired gas which reached the alveoli was larger than that calculated from the tidal volume less the dead space until a volume of about 300 cc. had been inspired. In other words, it was necessary to inspire a volume sufficient to wash out the dead space before this relationship was correct. These results are consistent with Henderson's idea that the inspired gas travels down the dead space in a central "spike". These findings are important in a complete evaluation of hypoventilation, controlled and artificial respiration.

Supervoltage Diagnostic Roentgenography. W. J. Tuddenham, M.D., John F. Gibbons, M.D., John Hale, M.S., and E. P. Pendergrass, M.D. (Department of Radiology, Hospital of the University of Pennsylvania). The authors have approached the problem of improving the diagnostic accuracy of the survey chest roentgenogram by defining the physical characteristics which govern the visibility of an image under the conditions of roentgenologic interpretation. They have found that the likelihood of the detection of a roentgenographic image is a function of the brightness gradient across the image border. Various methods of increasing this gradient have been explored. These studies have led to the development of supervoltage diagnostic roentgenography, a technique which is believed to have valuable clinical applications. More important, however, it demonstrates that the medical radiographer has at his disposal a far wider spectrum of useful radiation than has previously been supposed, and that by proper application of this widened spectrum, he can increase the effective-

ness of the Roentgen method in its clinical and research applications.

The Measurement of Renal Hemodynamics and Oxygen Consumption in Man to Estimate the Metabolic Contribution of Those Tubular Transport Systems Inhibited by Probenecid. EARL S. BARKER, M.D., JOHN KAPP CLARK, M.D., AND HAROLD G. BARKER, M.D. (Depts. of Medicine and Surgery, Medical School and Hospital, University of Pennsylvania). Probenecid (p-[di-n-propyl sulfamyl] benzoic acid) ("Benemid") has been demonstrated to depress tubular mechanisms for transport of para-aminohippurate (PAH), penicillin, phenolsulfonphthalein and uric acid. This blocking property has led to clinical use to enhance penicillin blood levels and promote uric acid excretion in gout, and thus additional information as to the action of the compound on the human kidney is of interest. The primary purpose of the present study, however, has been to utilize the blocking properties of probenecid to determine the extent to which those tubular transport systems contribute to the total metabolic need of the human kidney for oxygen. The degree to which renal oxygen utilization (Qo_2) may vary with functional activity has not been established unequivocally by either theoretical or experimental means.

Measurements of renal hemodynamics, tubular function, Qo_2, and electrolyte excretion were made before and during intravenous infusion of Probenecid in total dosage of 3 gm. in each of 5 normal subjects. Clearances of inulin (C_I), endogenous creatinine, and PAH (C_{PAH}) were determined. Catheterization of the right renal vein also permitted measurement of extractions of PAH and penicillin (E_{PAH}, E_{PEN}) and of renal arteriovenous oxygen difference $(A\text{-}R)o_2$. Renal blood flow (RBF) was calculated from the hematocrit and PAH Fick; Qo_2 from RBF and $(A\text{-}R)o_2$. One additional subject was studied to observe the effect of Probenecid on Tm_{PAH}.

The tubular blocking effect of Probenecid was illustrated by prompt and highly significant decreases in E_{PAH} (average fall from 93% to 55%), E_{PAH} and Tm_{PAH}. C_{PAH} fell parallel to E_{PEN}, but there was no significant change in C_I and RBF. There were also no significant changes in $(A\text{-}R)o_2$ or in Qo_2. Additional evidence is thus provided that the action of Probenecid is a highly specific one, rather than a depression (or "toxicity") of over-all tubular functions. The data also support the view that the bulk of oxygen consumed by the kidney is used for purposes other than external excretory or reabsorptive processes.

Histidine Synthesis in Yeast and Human Liver. M. J. COON, PH.D., AND L. LEVY, M.D. (Dept. of Physiological Chemistry, School of Medicine, University of Pennsylvania). Evidence has been presented previously from this laboratory that formate is the precursor of carbon atom 2 of histidine in yeast and that the imidazole ring of the amino acid is not derived from the corresponding ring of the purine bases. In recent experiments histidine and other amino acids were isolated from the proteins of yeast grown in the presence of acetate-2-C^{14} and unlabeled glucose. The C^{14} present in the histidine was found to be located exclusively in carbon atom 2 of the imidazole ring. Since formate has previously been shown to be the precursor of this carbon atom, it is concluded that the methyl carbon of acetate can serve as a source of "formate". It is apparent, however, that neither acetate nor glutamate and other compounds indirectly derived from acetate serve as precursors of the 5-carbon chain of histidine.

When yeast was grown in the pres-

ence of glucose labeled either uniformly or in carbon 1 with C^{14}, the isolated histidine was found to be radioactive. Chemical degradation of the histidine derived from glucose-1-C^{14} demonstrated that the carbon chain was labeled primarily in position 5, with the remaining C^{14} distributed among the carboxyl carbon, carbon 4, and the a + b carbons. Carbon atom 1 of glucose also contributes to the production of "formate" for histidine synthesis.

In other studies, human liver slices were incubated with formate-C^{14} and found to produce a labeled compound which was identified by paper chromatography as histidine.

BOOK REVIEWS AND NOTICES

THE MANAGEMENT OF PAIN. By JOHN J. BONICA, M.D., Director, Dept. of Anesthesia, Tacoma General and Pierce County Hospitals. Pp. 1533; 785 ills. Philadelphia: Lea & Febiger, 1953. Price, $20.00.

DR. BONICA has completed a masterful textbook. He has presented a concise, complete discussion of the fundamental aspects of pain, the various diseases and disorders in which pain is the major problem. He describes completely the methods employed in its management, with special emphasis on the use of analgesic block as an aid in the diagnosis, prognosis and therapeusis.

The contents of the book are divided into three parts. The first part includes the following fundamental considerations: the anatomical basis of pain, the neurophysiological basis of pain, the physiopathological basis of pain, the psychologic basis of pain, and the mental and physical effects of pain. This part takes up a small portion of the book, but is the most valuable part because of its completeness. The second part discusses the management of pain. In this section all phases of management are presented including not only block therapy, surgical therapy, psychologic therapy but also drug therapy, physiotherapy, orthopedic therapy and Roentgen therapy. The third section of the book presents the pain syndromes, such as neuralgias, causalgia and other reflex dystrophies, pain associated with peripheral vascular disease, pain of somatic origin and pain of visceral origin and allied disorders.

This is a valuable book and Dr. Bonica should be congratulated for his excellent presentation. "The Management of Pain" should be included in the libraries of all physicians.

L. K.

SURGICAL PATHOLOGY. By LAUREN V. ACKERMAN, M.D., Washington University School of Medicine. Pp. 836; 936 ills. St. Louis: C. V. Mosby, 1953. Price, $14.50.

DR. ACKERMAN has written a textbook in surgical pathology which, if not the most complete, is certainly the most refreshing of any that has been published in the last several years. In the past, texts of this type have drawn so heavily from pre-existing works that they give the impression of being simply a reorganization or reinterpretation of old material. In the present volume the author appears to depend extensively upon his own background as a surgical pathologist and having had a wide experience in this field what he has written has an authoritative appeal.

The lack of thoroughness and completeness is a serious criticism if the book is to be used by medical students and pathologists. For those who still believe that there is such a thing as a separate course in surgical pathology, this reviewer feels that there are many subjects which are casually treated and some, at least, which are completely omitted. I heartily endorse the book for use by clinicians, especially those who are preparing for board examination.

E. A.

ANNUAL REVIEW OF MEDICINE, VOLUME 4, 1953. Edited by WINDSOR C. CUTTING, M.D., and HENRY W. NEWMAN, M.D. Pp. 452. Stanford, California: Annual Reviews, 1953. Price, $6.00.

THIS volume is similar to its predecessors in that a broad range of medical topics is covered by competent authorities in the respective fields. The subjects reviewed include the diseases of most of the major systems. In addition, there are sections on infectious diseases, nutrition, allergy, neoplasms, vascular diseases of the brain, psychiatry, physical agents and trauma (burns and freezing), radiology, obstetrics, tropical diseases and plastic surgery (wound care and skin grafting). An annotated list of reviews in medicine completes the current edition.

C. Z.

HANDBOOK OF ORTHOPAEDIC SURGERY. By ALFRED R. SHANDS, JR., M.D., Medical Director of the Alfred I. Dupont Institution of the Nemours Foundation, Wilmington, Delaware, 4th ed. Pp. 644; 192 ills. St. Louis: C. V. Mosby Co., 1952. Price, $8.00.

THIS text was first edited in 1937, and, in the opinion of this author, it has always been considered excellent for teaching of orthopedics and fracture fundamentals to medical students, nurses and physiotherapists. The present edition is certainly no exception. The reproduction of the sources as roentgenogram, and not as drawings is an excellent change in this edition. The illustrations are well done.

In conclusion, I feel that this is one of the best handbooks in orthopedics, and its read-

ing should be mandatory for all medical students. A. S.

MEDICAL JURISPRUDENCE. By I. GORDON, M.B., CH.B., R. TURNER, M.B., CH.B., and T. W. PRICE, PH.D., LL.B. (Cantab), University of Cape Town. 3rd ed. Pp. 944; 143 ills. London: E. & S. Livingstone, Ltd., 1953. (Williams & Wilkins, Baltimore, U. S. Agents.) Price, $13.50.

AN up-to-date volume which discusses and explains the medicolegal problems facing the average physician should be received by the medical profession with the greatest enthusiasm. Written in language understandable to those not skilled in the field of law, it has the ability to retain the attention of one unaccustomed to legal technicalities and terminology.

Of interest and value to the lawyer as well as the physician is the selective list of actual cases touching upon the given point under consideration. Many of these cases are recited in factual detail which not only lends interest but also serves to clarify the situation in the mind of the reader. Wisely, the authors augment the usefulness of the book by including pertinent English and American citations as well as South African cases.

The scope of the book is amazingly extensive. From its first chapter dealing with the legal system in South Africa, through an intensive discussion of the legal aspects of a physician's practice, both in the fields of criminal and civil law, it is pleasingly thorough. The illustrative material adequately supplements the text.

In my opinion the book deserves wide circulation. It should enjoy a prominent place in the library of the physician as well as the lawyer. S. F.

ATOMIC MEDICINE. Edited by CHARLES F. BEHRENS, M.D. 2nd ed. Pp. 632; 134 ills. Baltimore: Williams & Wilkins, 1953. Price, $11.00.

ALL physicians should welcome the appearance of the second edition of this important work. Extensive and active research in the field, as well as the declassification of much of this and earlier material, called for a new edition and the 19 contributors have adequately met this challenge. There is a new chapter on classification and dosimetry of radioisotopes and many parts of other chapters have been extensively revised or entirely rewritten. Doctor Behrens is to be congratulated on this well-edited volume. R. K.

A BIBLIOGRAPHY OF THE WRITINGS OF DR. WILLIAM HARVEY 1578-1657. By GEOFFREY KEYNES, M.D., D.Litt., F.R.C.S. 2nd Ed. pp. 79; 21 ills. New York: Cambridge Univ. Press, 1953. Price, $10.00.

DURING the quarter century that has passed since the appearance of the first edition of this Bibliography, which incidentally was sold out in a few weeks, a surprising number of recorded copies has been added, though the list is not yet complete, even for the holdings of the libraries included. Interest in Harvey and his period has continued unabated: yes, even increased in recent years, and hitherto unsolved questions either explained or elucidated. It is not surprising, then, to see that considerable new material has been added to the text as one may infer from the dates in the footnote references.

Two portraits, one done during the time of Harvey's great work on the circulation and recently discovered by the author, another etched just before the appearance of his other major scientific achievement, *De Generatione Animalium*, are samples of the valuable inclusions in this new edition. For students of Geriatrics the two offer interesting comparisons. Much more could be added to demonstrate the value of this new edition to libraries and students of the period. E. K.

SEX: METHODS AND MANNERS. By LOUIS BERG, M.D. and ROBERT STREET. Pp. 249; 10 ills. New York: McBride Co., 1953. Price $3.50.

THE sexual incompatibilities which play such an important part in disrupting otherwise satisfactory marriages, usually stem from inadequacies in sex techniques or from misconception as to what represents normal sexual practices. The authors of this book contend that these problems can be prevented or corrected.

Normal adult sexual behavior is defined and described and the entire sex act is discussed in detail with particular attention being directed toward the methods for producing female orgasm. In contrast to most such discussions, however, the practical mechanics of precoital stimulation and coital techniques are described rather than only hinted at. There is room for disagreement with the importance they attach to the clitoris and clitoral

orgasm which many psychiatrists believe to be less desirable than a vaginal climax or even abnormal.

This book, prepared primarily for lay readers, ought to prove helpful as resolving sexual difficulties if it is properly used. Because its approach is so frank and open, the problems of many patients might be enhanced unless a preliminary period of exploration and discussion of the problem precedes their study of the text. J. W.

EINFÜHRUNG IN DIE AUDIOMETRIE. By HANS KIETZ, DR. ING. UND HANS E. ZANGEMEISTER, DR. MED. Pp. 180; 95 ills. Wiesbaden: Verlag für angewandte Wissenschaften, 1953. Price, DM 18.80.

THIS book gives a detailed discussion of the techniques and practical application of routine audiometry. In addition, it touches upon the more advanced fields, such as, the methods of difference limen determinations. Most illustrations are well chosen. On page 14, the audiogram of a case of tubal catarrh is unusual. The bone conduction curve for the middle tones is at the -10 to -20 level, while by air conduction, the loss is 70 db. On page 43, the bone conduction threshold is too low for a case of nerve degeneration. M. S.

HUMAN NEUROANATOMY. By OLIVER S. STRONG, Late Professor of Neurology and Neurohistology and ADOLPH ELWYN, Associate Professor of Neuroanatomy, College of Physicians and Surgeons, Columbia University. 3rd ed., Pp. 481; 357 ills. Baltimore: Williams & Wilkins Co., 1953. Price, $7.50.

DR. ELWYN has thoroughly revised and brought up-to-date this excellent text. The plan of organization is unchanged, and the book retains its position as one of the best among the many neuroanatomical texts.

Figure references given on the outline of the brain stem (Figures 182 and 284), to show levels of the transverse sections which follow, have been corrected. Thirty-four new figures are included in this edition.

Several sections of the text have been completely rewritten. Particular attention has been given in the revision to nerve regeneration and to the reticular formation. Similarly, the sections dealing with the cerebellum, diencephalon and cerebral cortex have been reworked and brought up-to-date with the findings resulting from neurophysiological research.

Although quite aware that most courses in neuroanatomy do not include the study of the gross morphology of the brain, it is regrettable that Dr. Elwyn has not included more on gross structure. Certainly a thorough knowledge of the gross anatomy of the brain is essential for the localization of pathology of the brain, and to correlate the neurological and roentgenological findings with the main nervous pathways involved in a pathological process. D. K.

MULTIPLE MYELOMA. By I. SNAPPER, M.D., Director, Medical Education, Cook County Hospital, Chicago, LOUIS B. TURNER, M.D., Res. Asst. in Med., Mt. Sinai Hospital, New York, and HOWARD L. MOSCOVITZ, M.D., Resident, Mt. Sinai Hospital, New York. Pp. 168; 43 ills., 1 in color. New York: Grune & Stratton, 1953. Price, $6.75.

THIS outstanding monograph is based on the extensive experience which Dr. Snapper and his colleagues have had with multiple myeloma. Chapters deal with the myeloma cell; the peripheral blood picture; with the clinical, roentgenologic and pathologic aspects, respectively; and the interesting metabolic abnormalities associated with the disease. There are also excellent sections on differential diagnosis and the present status of treatment.

This thorough, lucidly written dissertation is highly recommended to anyone interested in multiple myeloma. C. Z.

PROGRESS IN BIOPHYSICS AND BIOPHYSICAL CHEMISTRY. Edited by J. A. V. BUTLER AND J. T. RANDALL, University of London. Volume 3. Pp. 369. London: Pergamon Press Ltd., 1953 (Academic Press, New York). Price, $9.50.

THIS is a review of recent progress in selected biophysical subjects. The following items have been included: Autoradiography, polarized ultraviolet microspectography and molecular structure, infra-red spectra of biologically important molecules, photochemical studies on viruses, mechanisms of biological action of ultraviolet and visible radiations, application of the theory of the ionic double layer to colloidal systems, microspectrometry of living and fixed cells, methods of determining the form and dimensions of particles in solution and transport processes and electrical phenomena in ionic membranes. The usual high standards of presentation are preserved. M. O.

THE LOW FAT DIET COOK BOOK. By DOROTHY M. HILDRETH AND EUGENE A. HILDRETH, M.D. Pp. 136. New York: Medical Research Press, distributed by Grosset & Dunlap, 1952. Price, $2.95.

SEVERAL years ago Dr. Hildreth conducted experiments on himself and some of his colleagues concerning the effect of dietary restriction of fatty foods on blood cholesterol levels. Mrs. Hildreth, a trained dietitian, after several weeks of living with a husband on a low fat diet, was convinced that she had better do some experimenting, attempting thus to restore some of the pleasures of eating to her somewhat dejected spouse. The results of these experiments are contained in this book. The importance of limiting both vegetable and animal fat is recognized, and the plan of presentation is such that it is possible to select diets ranging from 10 grams of fat upwards. Many very practical suggestions are included (for example, low-fat gravy and mayonnaise), and the plan of presentation of the diets is such as to achieve a maximum of simplicity for the patient and his wife. It is the best book for the purpose known to the reviewer. T. D.

RYPINS' MEDICAL LICENSURE EXAMINATIONS. TOPICAL SUMMARIES AND QUESTIONS. Edited by WALTER L. BIERRING, M.D., with the Collaboration of a Review Panel. 7th ed. Pp. 856. Philadelphia: J. B. Lippincott Co., 1952. Price, $8.00.

THIS seventh edition of a book originally written and revised three times by the late Harold Rypins, M.D., and, since the fifth edition, under the editorial supervision of Dr. Bierring, should continue to hold its position of popularity as a means of reviewing for State Board examinations. This edition retains the original plan of separate summaries of each subject and actual questions based on the essential facts contained in the summaries. The table of contents is divided into two parts: Part I, Basic Medical Sciences, includes Anatomy, Physiology, Biochemistry, Microbiology, Pathology, Pharmacology; Part II, the Clinical Sciences, includes Surgery, Medicine, Obstetrics and Gynecology, Preventive Medicine and Public Health, Psychiatry. The chapters on Biochemistry, Microbiology, and Preventive Medicine and Public Health have been completely revised. The undergraduate student will find himself provided with a compact and orderly presentation of the various fields of medicine, and he will be able to obtain from its pages a dependable review of the material covered in the medical course. T. D.

DIE BEURTEILUNG DER ZURECHNUNGSFÄHIGKEIT. EIN VORTRAG. By KURT SCHNEIDER, University of Heidelberg. 2nd ed. Pp. 36. Stuttgart: Georg Thieme Verlag, 1953. (Grune & Stratton, New York, U. S. Agents). Price, DM 2.70.

THE author recounts a lecture, with a few notes, dealing with the subject of responsibility for crime according to the German code and with the provisions for omitting or mitigating the punishment in cases of supposed mental illness. An analysis of this part of the code and criticisms of some of its provisions are included, together with certain questions which might be put to the expert which seem to be presumed in it and which cannot be answered by him with accuracy. "You should mistrust an expert who can answer too much." The text is illuminating and is interesting for comparison with the common law, or the statute, or the codal law in some American jurisdictions. M. M.

THE COLLECTED PAPERS OF OTTO FENICHEL. Collected and edited by DR. HANNA FENICHEL and DR. DAVID RAPAPORT. Pp. 408. New York: W. W. Norton & Co., 1953. Price, $6.50.

THIS is the first volume of a series of two on the psychoanalytical writings of an outstanding worker in this particular field. Dr. Fenichel was a younger contemporary of Freud whose writing and thinking was clear and dependable and much appreciated. This volume contains thirty-four papers arranged in order of their appearance in the literature. They range over the field of theory and technique and are recommended to the physician with special interest in psychoanalytic psychology. O. E.

REACTION TO INJURY. PATHOLOGY FOR STUDENTS OF DISEASE. VOLUME II. By WILEY D. FORBUS, M.D., Prof. of Pathology, Duke University. Pp. 1110; 836 ills., 54 in color. Baltimore: Williams & Wilkins Co., 1952. Price, $20.00.

PHYSICIANS and teachers who have used Volume I of Dr. Forbus' Opus (published in 1943) will welcome the appearance of this book containing Parts III and IV of the total Reaction to Injury treatise. Introductory

and orienting material had constituted Part I. and Resistive Reaction to Injury, Part II of the earlier book. In the present volume, Parts III and IV present the other 2 of the 3 basic reaction types, Submissive and Adaptive reactions respectively. As in Volume I, the purpose of the author has been to aid students in anchoring themselves to "the solid rock of pathological anatomy, functionally interpreted", and this purpose has been admirably achieved. The well written text (manifesting clearly the long teaching experience of the author) is supplemented by a wealth of excellent photographs and diagrams. Basic clinical material is included along with the pathological for correlative purposes, and to serve the student of medicine continuously throughout all his clinical studies, not just during his course in general pathology. It is claimed, further, that sufficient clinical and historical data are presented to make it unnecessary for a second year student to use a textbook of general medicine. With this claim the reviewer stands in disagreement, based on his experience as a clinical teacher. This is particularly so because of the lack of up-to-date material. As an example of this, the section on pernicious anemia contains only 5 references, out of a total of 55, more recent than 1940, and none subsequent to 1946. Thus vitamin B_{12}, discovered in 1948, is not mentioned at all, and this means, of course, that the fuller understanding of pathogenesis related to this discovery is likewise lacking. Similar examples could be provided in connection with other diseases. Despite this drawback, however, Dr. Forbus' book does provide students and young doctors with "a new highway to both old and new places". T. D.

A Source-Book of Medical Terms. By Edmund C. Jaeger, D.Sc., Formerly, Head of Department of Zoology, Riverside College. Pp. 145; 86 ills. Springfield Ill.: Charles C Thomas, 1953. Price, $5.50.

A previous book on Biological Names and Terms by this author was excellent for its purpose, but the present venture is not so fortunate simply because the writer is a zoologist and not trained in medicine. It is regrettable that science is so specialized that it is difficult for even a zoologist to step over the boundary into medicine. This is evidenced in this book by many of the definitions and examples; by the absence of many medical terms and the presence of many terms not of medical interest. For example, one fails to find the words measles, pertussis and grippe, while such unfamiliar terms as anhelation, acathetic, palirrhea, poltophagy and zestocausis are present.

A single selection from the book may help to justify these criticisms. Will not a medical student who looks up the source of the word anemia be amazed to find following the base: anem- the word anemone, the wind flower, with examples anemonism, anemopathy, anemophilous, anemophobia and anemotaxis. Anemia comes second with the examples anemic, anemize, anematize and anematosis.

No doubt these terms are in the dictionary but few of them are in current medical use. This book cannot be recommended to students or doctors of medicine. O. P.

Pathology. Edited by W. A. D. Anderson, M.D., Prof. of Pathology, Univ. of Miami School of Med. 2nd ed. Pp. 1393; 1241 ills., including 10 color plates. St. Louis: C. V. Mosby Co., 1953. Price, $16.00.

This is the first revision of Dr. Anderson's original volume published in 1948. Like the first edition it is a collaboration of 33 writers, most of them eminent authorities on the particular subjects which they contribute.

A first revision is generally a better book than its predecessor and this is no exception. It is the first text in pathology to give adequate consideration to the endocrine glands, skin and to bone and joints. Some of the special sections such as that on the effects of radiation, chemical injury and the effects of injurious physical agents are superb. Like the original it still suffers by virtue of its magnitude and an attempt to put the less important material in fine print, in my estimation, has not helped this fault. A book of basic principles must be written as such. A text cannot be made both thorough and basic by the simple device of using two sizes of type. E. A.

Renal Function. Transactions of the Third and Fourth Conferences, New York City, 1951 and 1952. Edited by Stanley E. Bradley, M.D. 1951: Pp. 210, 80 ills. 1952: Pp. 189, 47 ills. New York: Josiah Macy, Jr. Foundation, 1952 and 1953. Price: $3.50, each volume.

The multiprofessional approach in advancing medical knowledge which has characterized previous Macy Foundation Conferences was also the basis of the two conferences

carefully transcribed for these volumes. Included in the 1951 conference were the following subjects: "Passage of Substances Across Capillary Walls", "Intrarenal Pressure and Renal Blood Flow", "Physical Factors in Relation to Electrolyte and Water Excretion", "Use of the Artificial Kidney", "Tubular Secretion of Potassium and Acid", and "Enzymatic Processes in Tubular Secretion and Absorption". In the 1952 conference there were included: "Ion Exchanges Between Extracellular and Intracellular Fluids", "Cation Exchanges in the Renal Tubular Epithelium", "Ion Transport Across Living Membranes", and "Water and Ion Movements Across Intestinal and Renal Epithelium". The discussors of these subjects are outstanding experts in their fields, and the transcripts provide the reader with excellent summaries of recent trends in basic understanding of renal function and disease. T. D.

THE BALLISTOCARDIOGRAM. A DYNAMIC RECORD OF THE HEART BEAT. By JOHN R. BRAUNSTEIN, M.D., PH.D., Assoc. Prof. of Biophysics and Asst. Prof. of Medicine, Univ. of Cincinnati. Pp. 84; 41 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $3.00.

THIS monograph has been prepared from lectures delivered by the author in the Spring of 1951. There has been no attempt to cover the entire field of ballistocardiography, even though it is a small one. The author has succeeded, however, in presenting the basic facts in a very accurate and instructive fashion. After a discussion of historical aspects, and a description of modern instruments, there follows a brief consideration of the ballistocardiographic complex and its respiratory variation, the abnormal B.K.G. pattern, the calculation of the cardiac output, the clinical significance of abnormal pattern and of abnormal output, the vector-ballistocardiogram, and a very valuable appendix. It is a volume which should prove to be extremely useful as an introduction to the subject, and the reader, who had not previously become fascinated by the potentialities of ballistocardiography, will find it difficult to resist the appeal of a subject within which "is locked the secret of the dynamic action of the heart". T. D.

RHEUMATIC FEVER. A SYMPOSIUM. Edited by LEWIS THOMAS, M.D., American Legion Memorial Heart Research Protessor in the Departments of Pediatrics and Medicine, University of Minnesota. Pp. 349, 57 ills. Minneapolis: University of Minnesota Press, 1952. Price, $10.00.

THIS book contains the papers and discussions which were presented during a three-day symposium held at the University of Minnesota during the latter part of 1951. A representative group of investigators who have made important contributions to the information concerning rheumatic fever were brought together from various parts of the country and the program designed in the hope that the present status of all major aspects of the problem would come under discussion. The result has been a book of proceedings which should be of great value to the investigator, teacher and practitioner of medicine. The subjects covered range from epidemiologic and etiologic phases, through clinical features and closely related clinical subjects, to a final consideration of prevention and management, including the place of cortisone and corticotropin and the surgical problem in rheumatic valvular heart disease. An extensive bibliography is appended. Unfortunately there is no index. T. D.

CLINICAL DISORDERS OF THE HEART BEAT. By SAMUEL BELLET, M.D., Director, Division of Cardiology, Philadelphia General Hospital and of the Division of Cardiovascular Diseases, Graduate Hospital, University of Pennsylvania. Pp. 373; 164 ills. Philadelphia: Lea & Febiger, 1953. Price, $8.50.

KNOWLEDGE of the diagnosis and treatment of the cardiac arrhythmias has always been of great importance to the general practitioner, internist and cardiologist. Recent advances in thoracic and cardiac surgery have made such knowledge increasingly important to the anesthesiologist and surgeon as well. Dr. Bellet's presentation of this subject should prove to be of great value to each of these groups as a volume for reference and for study. Throughout its pages the author's many years of experience in postgraduate teaching are readily apparent in the clarity of the discussion and in the emphasis upon the practical aspects of each phase of the subject. Numerous boxed summaries have been included to make available a quick review of important points. The illustrations are well chosen and clearly reproduced. It is a volume to be highly recommended to all physicians as an authoritative, concise, well written, and up-to-date presentation of the disorders of cardiac rhythm. T. D.

MEDICAL TREATMENT OF DISEASE. OXFORD MEDICINE, VOL. 8. Edited by HENRY A. CHRISTIAN, M.D., Physician-in-Chief, Emeritus, Peter Bent Brigham Hospital, Boston, Mass., DALE G. FRIEND, M.D., Consultant in Medicine, Sturdy Memorial Hospital, and MAURICE A. SCHNITKER, M.D., Chief of Staff, Maumee Valley Hospital. New York: Oxford University Press, 1953. Price, $25.00.

THIS loose-leaf text is designed, as is the Oxford Medicine series, so that new material can be added and old material subtracted. While this has obvious advantages, it should be noted that therapy is advancing so rapidly, that even the initial publication has fallen behind. This is especially true in the antibiotic field where erythromycin, the nitrofurans and others are not included.

In general, the field of disease treatment is covered in a detailed and clear manner with the necessary precautions given sufficient emphasis. The use of psychiatric aid in treatment is mentioned, but in a rather deprecatory manner.

The basic defect in this book is common to most similar texts. The approach to therapy is as stated in the title 'Treatment of Disease', instead of treatment of the patient with disease. W. S.

SPATIAL VECTORCARDIOGRAPHY. BY GEORGE E. BURCH, M.D., F.A.C.P., Henderson Professor of Medicine, J. A. ABILDSKOV, M.D., Instructor in Medicine, and JAMES A. CRONVICH, M.S., Professor of Electrical Engineering, Tulane University. Pp. 173; 121 ills. Philadelphia: Lea & Febiger, 1953. Price $5.00.

THE material contained in this volume was displayed among the scientific exhibits at the meeting of the American Medical Association in June, 1952. It contains primarily a brief, concise presentation of the concept involved, and the principles and methods of recording, followed by a summary of certain aspects of studies conducted at Tulane since 1945. It is intended primarily for those not engaged in research in this field. It is the opinion of the authors that the equilateral tetrahedron is the most suitable reference frame for routine recording, and the very cogent reasons for this opinion are well presented. It is emphasized that the spatial vectorcardiogram does not replace the electrocardiogram, and that it is of limited supplementary value. It is not yet suitable for general clinical application since it is still in the experimental stage. It is, however, "an interesting and important aspect of electrocardiography, and careful and thorough work should be encouraged and supported, for practical applications may be reasonably expected in the near future".

This volume is highly recommended to all cardiologists and physiologists who desire to acquaint themselves with the present status of investigation into a field holding promise of considerable future expansion. T. D.

NEW BOOKS

Acute Pulmonary Edema. Modern Medical Monographs No. 10. BY MARK D. ALTSCHULE, M.D., Asst. Prof. of Medicine, Harvard Medical School. Pp. 68. New York: Grune & Stratton, Inc., 1954. Price, $3.50.

THIS is a practical little volume on an important subject. Written for students, it will be equally helpful to practicing physicians because of its simple, clear-cut presentation of the subject. There are chapters on clinical manifestations including the differential diagnosis; on basic physiologic considerations; on pathological physiology; and on treatment. The book is well recommended. R. K.

Physiological and Therapeutic Effects of Corticotropin (ACTH) and Cortisone. BY DWIGHT J. INGLE, PH.D., AND BURTON L. BAKER, PH.D. Pp. 172; 17 ills. Springfield, Ill.: Charles C Thomas, 1953. Price, $5.50.

THE important physiologic and therapeutic effects of ACTH and cortisone are reviewed in this monograph, which is written by outstanding laboratory investigators in this field.

The work offers a brief but thorough orientation into basic aspects of adrenal cortical function, and is recommended to physicians for this reason. It is less valuable with regard to therapy since some of the promise of these substances for certain clinical entities has faded with further experience. C. Z.

Orthopädische Konstruktionen. BY PROF. DR. FRANZ SCHEDE. Pp. 98; 141 ills. Stuttgart: Georg Thieme Verlag, 1953. Price, DM 8.

Die Wirbelsäulentuberkulose und ihre Differentialdiagnose. BY DR. J. E. W. BROCHER, PRIV.-DOZENT, GENF. Pp. 272; 376 ills. Stuttgart: Georg Thieme Verlag, 1953 (Grune & Stratton, New York, Agents for U.S.A.). Price, DM 78.

Veterans Administration—Army—Navy Transactions of the 12th Conference on the Chemotherapy of Tuberculosis, February 9-12, 1953. Pp. 430. Washington: Veterans Administration, 1953.

THE material contained in this volume was presented at the meeting held in Atlanta, Georgia,

on February 9 to 12, 1953. There are major sections on pulmonary tuberculosis (including emergence of resistance, tuberculous sinuses, and miliary-meningeal tuberculosis); surgical and laboratory studies of pulmonary tuberculosis; and miscellaneous topics.

Everyone interested in this important health problem will find the report of the 12th Conference a valuable reference work. C. Z.

Medical Clinics of North America, Philadelphia Number, November, 1953 Pp. 323; 32 ills. Philadelphia: W. B. Saunders Co., 1953. Price, $15.00 per annum.

THIS volume of the Clinics, quite up to the usual high standard of their content, has this distinctive feature: it is a worthy tribute dedicated to Dr. O. H. Perry Pepper, Emeritus Professor of Medicine, University of Pennsylvania. It contains 22 articles, written by 27 contributors, former colleagues and students of Doctor Pepper and active in 9 medical schools in various parts of the country. There is a foreword by Dr. A. N. Richards, Emeritus Professor of Pharmacology and Former Vice-President for Medical Affairs in the University of Pennsylania.

R. K.

NEW EDITIONS

The Fundamentals of Radiography. 8th ed. Pp. 100; 45 ills. Rochester, New York: Medical Division, Eastman Kodak Co., 1953. Free, on request.

THIS is a new edition of the book which was first published in 1938. It provides a readily understandable but authoritative presentation of the basic principles of Roentgen-ray exposure, technique, and processing, and a practical guide for application of the principles. The book is well illustrated. It will be of value to any physician who is involved in diagnostic radiology, whether on a small or large scale, for himself, his students and technical assistants. H. S.

Ophthalmic Surgery. By J. MELLER. 6th ed. Pp. 529; 287 ills. New York: The Blakiston Co., 1953. Price, $12.00.

Textbook of Medical Treatment. Edited by D. M. DUNLOP, M.D., Prof. of Therap. and Clin. Med., Univ. of Edinburgh; L. S. P. DAVIDSON, M.D., Prof. of Med. and Clin. Med., University of Edinburgh, and SIR JOHN MCNEE, M.D., Regius Prof. of Practice of Med., University of Edinburgh. 6th ed. Pp. 1023; illustrated. Edinburgh: E. & S. Livingstone, Ltd., 1953 (Baltimore: Williams & Wilkins, U. S. Agents). Price, $9.50.

THE fact that, since its first appearance in 1939, this work has reached its sixth edition, is ample testimony of its value and excellence. The text has been thoroughly revised and there are new chapters on Chemotherapy, Rehabilitation, The Treatment of Poisoning, and The Chemotherapy of Malignant Disease. The 26 contributors are all recognized authorities in their field. The book should find a wide appeal.

R. K.

A Primer of Cardiology. By GEORGE E. BURCH, M.D., Henderson Prof. of Medicine, Tulane University of Louisiana School of Medicine. 2nd ed. Pp. 339; 214 ills. Philadelphia: Lea & Febiger, 1953. Price, $5.50.

STUDENTS, practitioners and teachers will welcome this second edition of an extremely practical book. The reviewer, who is not a cardiologist but who has been interested in cardiology for a long time, testifies willingly to the excellence of this primer. The work has been extensively revised and brought up-to-date. The excellent illustrations include a number of new and improved ones. The book is heartily recommended. R. K.

Die Zuckerkrankheit. Leitfaden für Studierende und Arzte. By PROF. DR. FERDINAND BERTRAM. 4th ed. Pp. 175; 25 ills. Stuttgart: Georg Thieme Verlag, 1953. Price, DM 19.80.

THIS is "an outline for students and physicians" that is now in its 4th edition, since the work was first published twenty years ago. It presents in concise form a very complete review of all aspects of this important condition. The subject matter is arranged and set up in an excellent way that could well be copied by English writers. The views expressed are sound and in the main acceptable to most authorities in the field. Physicians and students, who read German, will find this an excellent text for study and handy reference. R. K.

Lehrbuch der Konstitutionstherapie. By DR. MED. BERNHARD ASCHNER. 7th ed. Pp. 713. Stuttgart: Hippokrates-Verlag Marquardt & Cie., 1953. Price, DM 46.50.

THE author defines "Konstitutionstherapie" as (a) treatment of the whole man and (b) the application of the whole of medicine: that is, everything that has proved helpful in treatment procedures in all times and by all peoples. After browsing through some hundreds of pages of text, one has the impression of time spent in an old attic with dust-covered remnants from a forgotten past that the hoarder thinks might still be useful. One wonders what prompted the 7th edition of a work whose 6th edition appeared nineteen years ago. There may be some wheat but there is altogether too much chaff in this bag to make it worth unpacking. R. K.

Ostliche Weisheit und Westliche Psychotherapie. By GUSTAV SCHMALTZ. 2nd ed. Pp. 164. Stuttgart: Hippokrates Verlag Marquardt & Cie., 1954. Price, DM 8.50.

THE author discusses certain aspects of oriental philosophies in relation to their use in psychotherapy. A considerable portion of the book consists of quotations from the writings of philosophers of India, China and Japan. Psychiatrists who read German will find this little book both interesting and stimulating. R. K.